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ON THE

RATIONS PRODUCED IN THE LARGE INTESTINES OF DOGS BY THE AMŒBA COLI, BY HEAT, AND BY VARIOUS CHEMIC SUBSTANCES,

WITH NOTES ON THE ANATOMY AND HISTOLOGY OF THIS VISCUS.

BY

H. F. HARRIS, M.D.,
ATLANTA, GA.

A RESEARCH CARRIED ON UNDER THE AUSPICES
OF THE NATHAN L. HATFIELD PRIZE COMMITTEE OF THE COLLEGE
OF PHYSICIANS OF PHILADELPHIA.

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TO

JUDGE SAMPSON WATKINS HARRIS

AND

LUCY WATKINS HARRIS,

THIS LITTLE VOLUME

IS AFFECTIONATELY DEDICATED

BY THEIR SON,

THE

AUTHOR.

16000

TO

The Memory of

NATHAN LEWIS HATFIELD, M.D.,

THIS ESSAY

HONORED BY THE FIRST TRIENNIAL AWARD OF THE

NATHAN LEWIS HATFIELD PRIZE,

IS PUBLISHED BY THE

TRUSTEES OF THE MEMORIAL FUND.

EXTRACT FROM THE MINUTES OF THE STATED MEETING OF THE COLLEGE OF PHYSICIANS, HELD MAY 1, 1901.

DR. WILSON moved that the College direct the Trustees of the Nathan Lewis Hatfield Memorial Fund to pay the award of five hundred dollars to DR. H. F. HARRIS, of Atlanta, Georgia, for his research entitled: "A Study of the Alterations Produced in the Large Intestines of Dogs by the Amœba Coli, by Heat, and by various Chemic Substances, with Notes on the Anatomy and Histology of this Viscus."

PREFACE.

THE experiments, the results of which are recorded in the succeeding pages, were begun in the spring of 1899, in the laboratories of the Jefferson Medical College Hospital, of Philadelphia. During the following summer the work was continued in the Laboratory of Experimental Pathology of the University of Vienna. For permission to work in the latter laboratory the writer is indebted to Geheimrath Prof. Dr. Knoll and to his very able First Assistant, Dr. Biedl, to whom he particularly desires to express his thanks for many kindnesses. In the early spring of the following year the investigations were resumed at the laboratories of the Jefferson Medical College Hospital, where every opportunity was afforded the writer to carry on his experiments by his honored former teacher and colleague, Prof. W. M. L. Coplin, who frequently took upon himself the burden of routine laboratory work, in order that the author might be free to pursue his studies. During the past winter the investigations have been carried on in the Laboratories of Pathology and Bacteriology of the Atlanta College of Physicians and Surgeons. In this connection the writer wishes to express his deep appreciation of the valuable assistance rendered to him, while working in the last-named laboratory, by Dr. C. E. J. Smith and by Mr. Leon Weis, at that time an undergraduate in the Atlanta College of Physicians and Surgeons.

Although during the periods mentioned the writer was almost constantly engaged in this work, it must be confessed that the results appear meagre and disappointing when the few substances experimented with are compared with the vast number of those capable of setting up abnormal processes in animal structures. Notwithstanding this, the author ventures to express the hope that these investigations may be of some value to future laborers in the field of pathologic histology, particularly as they seem to indicate that with the advance in technical methods it will be possible at no distant day to accurately determine the nature of all disease-producing causes by the character of the lesions induced in the tissues.

MARCH, 1901.

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PART I.

TECHNICAL METHODS.

PART I.

TECHNICAL METHODS.

IT has very often occurred that investigators in recording their experiments have failed to state in a distinct and clear manner the technical methods employed by them, and as a consequence subsequent observers have not infrequently failed, either wholly or in part, to corroborate their results. For this reason it appears to the writer that a brief résumé of the methods employed by him during the course of his work will not be without value.

Great care was always exercised to avoid causing unnecessary pain to the dogs experimented upon. Shortly before the use of any of the irritating substances that were administered to them the animals were invariably given a large hypodermatic injection of morphine, and in all instances where operative procedures were required, or where an unusual amount of pain would have resulted from the manipulations, ether was in addition exhibited. After the experiments were finished, if the animal did not die as a result, chloroform was given until death was produced. In all instances the animal was instantly opened following death, but in a few cases where the dogs died during the night a post-mortem examination was not made until the following morning. With great care, and always avoiding pressure or force of any kind upon the walls, the large bowel was removed, and without coming in contact with any fluid, or other substance, was immediately placed in a fixing solution. At the time of the beginning of these investigations numerous experiments were made to determine the best method of keeping the wall of the bowel stretched during the time that it was kept in the fixative, and in the subsequent alcoholic solutions, as it was found that as soon as the specimens were immersed the muscular structures contained within them always contracted and caused great distortion. After numerous trials the following plan was adopted: As soon as the intestine was cut open one of its ends was pinned to a thin piece of board by means of tacks, and then grasping the other end of the bowel the walls were stretched to a moderate degree; tacks were then fastened along and around its edges at whatever points were necessary to hold it in this position. It is, of course, true that the tissues in the immediate neighborhood of the tacks are not suitable for microscopic examination, but with a little care there was no difficulty in so placing them that the most interesting portions of the lesions were entirely unaffected.

At first a large number of different fixing solutions were tried, to enumerate all of which would be entirely profitless; suffice it to say that excellent results were gotten by the use of both Flemming's and Hermann's solutions, and also by the use of corrosive sublimate alone, and the various mixtures containing it. However, after much investigation the corrosive sublimate mixture of Bensley, employed by him for the study of the prozymogen granules in the cat's stomach, was found to be most generally applicable. The reasons for this selection are that while the osmic mixtures just referred to preserve the morphologic constituents of cells most admirably, it is impossible to obtain after their use some of the microchemic reactions of the granules of certain cells, and none of the other corrosive sublimate mixtures preserve the structure of the cells, and at the same time permit their chemic investigation so well as the mixture selected. Bensley's solution is made as follows:

One to two per cent. bichromate of potassium in water.
Saturate solution of corrosive sublimate in alcohol.

Equal parts of these two solutions are mixed together just before use, and the tissue is immersed in the mixture for from one-half to two hours. The tissues are next washed well in water, dehydrated, cleared, and embedded in paraffine in the usual way. When using large blocks of paraffine the writer has found that this substance does not harden properly when cooled rapidly, as is generally recommended, but that it assumes most excellent cutting consistency if kept at about 37° C. for a day or two. Sections are then cut; for this purpose the Minot-Blake microtome has recently been used, and with a sharp knife it certainly produces the most even and uniform sections that the writer has ever seen. After being cut the sections are spread and fastened to the slides by Ohlmacher's method; they are then thoroughly dried, the paraffine is dissolved off with xylol, the corrosive sublimate crystals are removed with tincture of iodine, and the sections are soaked in pure alcohol until the iodine is entirely removed. They are then ready for staining. The numerous solutions through which the sections were carried were kept in the staining jars devised by Coplin, which are so convenient that the writer thinks special mention should be made of them.

For the purpose of staining nearly all of the usual methods, and quite a number of special ones, were employed from time to time, but in every instance a greater or less number of sections were prepared by the following methods:

In order to obtain a general idea as to the state of the tissues, specimens were always first stained with hæmatein, the writer's solution of which is prepared as follows:

Hæmatoxylin	1 gm.
Alcohol	10 c.c.

The former is dissolved in the latter, and 500 c.c. of a saturated solution of alum in water is added. Boil, and while in this state add 0.5 gm. of mercuric oxide. In a few moments the solution turns to a dark, rich purple color, and the vessel containing it is then removed and cooled rapidly. After cooling the solution is filtered, and 4 per cent. of glacial acetic acid is added. This mixture keeps excellently, and although much cheaper it is in every particular equal to Mayer's acid hæmalum. The stain may be used in the concentrated form, but it is preferable to employ it greatly diluted with water, or, perhaps better, with an aqueous solution of alum, and to allow the section to remain in it overnight. In this way an almost pure nuclear stain is obtained, and one which can scarcely be surpassed by any of the coal-tar colors.

In many instances the specimens were counterstained with eosin after previous treatment in the hæmatein stain. The solution of eosin that the writer has constantly employed for a number of years is prepared by adding alcohol-soluble eosin and water-soluble eosin (the latter is also soluble in alcohol) to ordinary 95 per cent. alcohol to the point of saturation. It has been found that with a solution prepared in this way many of the morphologic elements of tissues may be readily differentiated from each other—as, for example, muscle and fibrous tissues are stained in such different tones of red that they may be told apart at a glance.

Picric acid is also an excellent counterstain for hæmatein; it makes the tissues look clearer than any other plasma stain.

For the purpose of especially studying the mitotic figures that are so abundant in the deeper portions of Lieberkuehn's crypts, and also for investigating the other nucleated structures in the tissues, Benda's hæmatoxylin method was found to be most serviceable. Counterstains may be also employed after sections have been colored in this way, but inasmuch as the stain is itself a most excellent one for the plasmatic structures of cells, this is generally unnecessary.

For the purpose of studying fibrous tissue there is perhaps no method that is altogether so satisfactory as Van Gieson's. Instead of Delafield's hæmatoxylin the writer always uses the acid hæmatein, to which reference has already been made; the latter solution is preferable, as the nuclei are alone stained by it. In tissues prepared in this way the connective tissue fibrils appear under the microscope with diagrammatic clearness, and the other structures are also well shown.

In all of these investigations it has been of great importance to determine the extent of the formation of mucin in the glands, and, thanks to that most eminent technologist, Mayer, we possess in his muchæmatein a most admirable reagent for the demonstration of this substance. This stain may be prepared directly from hæmatein, as was recommended by Mayer, but the solution devised by the writer is in every way as efficient, and much less expensive. It is made as follows:

Hæmatoxylin	0.2 gm.
Aluminium chloride	0.1 "
Glycerin	50 c.c.
Water	50 "

Mix and dissolve the first two ingredients in the last. Boil. While boiling add 0.2 gm. of mercuric oxide. The mixture very quickly assumes a dark purple color. It is then cooled and filtered. This stain may be employed in a concentrated form, or water may be added to it very largely before it is used. The mucin assumes almost exactly the same color as the staining solution—*i. e.*, it presents after treatment a beautiful rich purple hue; with the exception of the granules found in mucinoblasts no other structures found in the dog's intestine are tinted in this way by the stain.

One of the most useful combinations of these stains consists in treating sections with the hæmatein solution first, then washing off with water, staining next in muchæmatein, and after passing through water and alcohol finally counterstaining in an alcoholic solution of picric acid. When tissues are prepared in this way the nuclei have a dark brownish color, the mucin appears of a bright purple hue, and the surrounding protoplasmic structures are dyed in varying tones of yellow. Perhaps in no other way can such a general conception of the state of the entire intestinal wall be gained so clearly and so quickly as from an examination after the tissues have been stained in this way.

Inasmuch as the intestinal wall contains considerable quantities of elastic tissue, it was necessary in all instances to differentiate these structures in such a way that their condition might be properly examined into. In order to do this Weigert's stain for elastic tissue was in the beginning always employed, but later the following method was used:

During these investigations a series of accidents led the writer to discover the fact that hæmatein solutions, when prepared in a certain way, have a remarkable affinity for elastin, and that this substance may be differentiated clearly from other tissues by the employment of the peculiar stain in question; and, inasmuch as the results obtained by its use appear to be in some particulars superior to those gotten from Weigert's method, the former has been recently usually substituted for the latter. The stain is made in the following manner:

Hæmatoxylin	0.2 gm.
Aluminium chloride	0.1 "
Fifty per cent. alcohol	100 c.c.

Dissolve the hæmatoxylin and aluminium chloride, and then carefully bring the solution to a boil; 0.6 gm. of mercuric oxide is now slowly added, and as soon as the mixture assumes a dark purple color it is removed from the flame and cooled rapidly. The stain is filtered, and one drop of hydrochloric acid is added. A short time after cooling a flocculent precipitant is sometimes formed in the solution; this is immediately dissolved upon the addition of the hydrochloric acid. The stain should then be set aside for some weeks, as it will not, as a rule, give satisfactory results at once.

The writer has not been able to find the reason for this, but the change does not appear to depend upon the continued absorption of oxygen by the hæmatein, for the reason that no degree of artificial oxidation seems to quicken the result. It must be admitted that this stain is somewhat capricious in its "ripening," but after this has been once accomplished it appears to keep indefinitely. The stain is used by immersing thin sections of tissue in it for from five to ten minutes, and then washing off for about a minute in a 1 per cent. solution of nitric acid in alcohol; the acid alcohol is then thoroughly removed with pure alcohol, and the sections are cleared and mounted. The elastic tissue fibrils are stained a uniform dark purple hue, while the other tissues are colored in varying tones of red. This method seems to offer an advantage over that of Weigert, in that there is not so much tendency to color the neighboring fibrils of collagenous tissue, and that even in those cases where this does occur the tint is entirely different. This stain is so closely related chemically to Mayer's muchæmatein that the name *elashœmatein* naturally suggests itself for it. It may be of interest in this connection to remark that when tissues are treated with Mayer's mucicarmine and afterward with an alcoholic solution of nitric acid, any elastin that may be present stains much more brilliantly than do the other structures, and this method, as a consequence, may be used for differentiating between them. With both of these stains mucin is always decidedly colored, but inasmuch as this substance is rarely found in those localities where elastic tissue occurs, and is morphologically entirely unlike it, there is no possibility of confusing them.

Of all the methods for the demonstration of mucinoblasts[1] and plasma cells there is none which is, perhaps, so available for general work as the writer's carbol toluidin-blue, the reasons for this being that the stain is perfectly permanent, and, on account of its neutral reaction, does not injure the delicate nuclear network of cells. This stain is prepared by dissolving from 1 to 2 per cent. of toluidin-blue in a 2 to 4 per cent. solution of carbolic acid in water. Sections may be stained for from a half-minute to several days. Before and after staining the tissues should be always washed thoroughly in water, as this prevents the precipitation of particles of the dye that invariably occurs when the stain is brought directly in contact with alcohol. After washing the sections may be differentiated, especially if thin, in ordinary alcohol, cleared in xylol or cedar-wood oil, and mounted in the usual way, or this result may be, perhaps, better accomplished by treating them with Unna's glycerin-ether mixture diluted from five to ten times with water; in from five to ten minutes the process is completed and the section is then quickly washed in alcohol, cleared in cedar-wood oil or xylol, and mounted in balsam. In this way the granules in the mucinoblasts are colored red, while the finer particles lying in the protoplasm of the plasma cells assume a dark bluish color. This reaction is evidently due to differences in the chemic nature of the granules of these cells, and not, as Unna stated when speaking of his alkaline methylene-blue solution, to the presence of different coloring agents in the stain. It should here be said that the glycerin mixture of Unna above referred to cannot be prepared very conveniently without the apparatus which is usually only found in a chemic laboratory, and that the mixture had best be purchased from Gruebler, or from some of the microscopic dealers in this country who supply his reagents.

In many instances, especially where necrotic changes are in progress, it becomes of much importance to determine if the tissues react to dyes in the usual way—*i. e.*, if those structures that normally take the basic stain and those that are colored in health by acid dyes still retain these peculiarities in a normal manner; this important point can be determined in no better way, nor more clearly, than by staining the sections for from a few minutes to several hours in the carbol toluidin-blue solution already referred to, afterward washing off with water, then quickly in alcohol, and finally immersing the tissues for a few seconds in the alcoholic solution of both water- and alcohol-soluble eosin, to which reference has been made. After the treatment in this way the section is again rinsed in alcohol, cleared in xylol or cedar-wood oil, and finally mounted in balsam. All those structures that have affinity for basic dyes are stained blue, while the eosin colors the remaining tissues in varying tones of yellowish-red. It is of importance in all cases that the eosin solution should be an alcoholic one, as it does not abstract the basic dye so readily, and, in addition, produces in the tissues differential effects that are never obtained when the stain is applied dissolved in water.

---

[1] The word "mucinoblast" is constantly employed in this essay in describing those peculiar cells to which Ehrlich gave the name of mast cells. If we may rely on microchemic reactions the granules in these cells consist of mucin, as the writer has shown in another place, and the former name therefore appears much more appropriate than the latter.

Fibrin has been sought for by staining the tissues with aniline gentian violet in the way recommended by Weigert. In carrying out the process the usual steps have been followed, but it may be mentioned that the writer has found that the staining solution may be preserved indefinitely by adding to it from 1 to 2 per cent. of tincture of iodine in which a small quantity of corrosive sublimate has been dissolved. It is quite possible, though it has not been tried, that an alcoholic solution of iodide of mercury, or even of corrosive sublimate, would accomplish the same result.

PART II.

ANATOMY AND HISTOLOGY OF THE LARGE INTESTINE OF THE DOG.

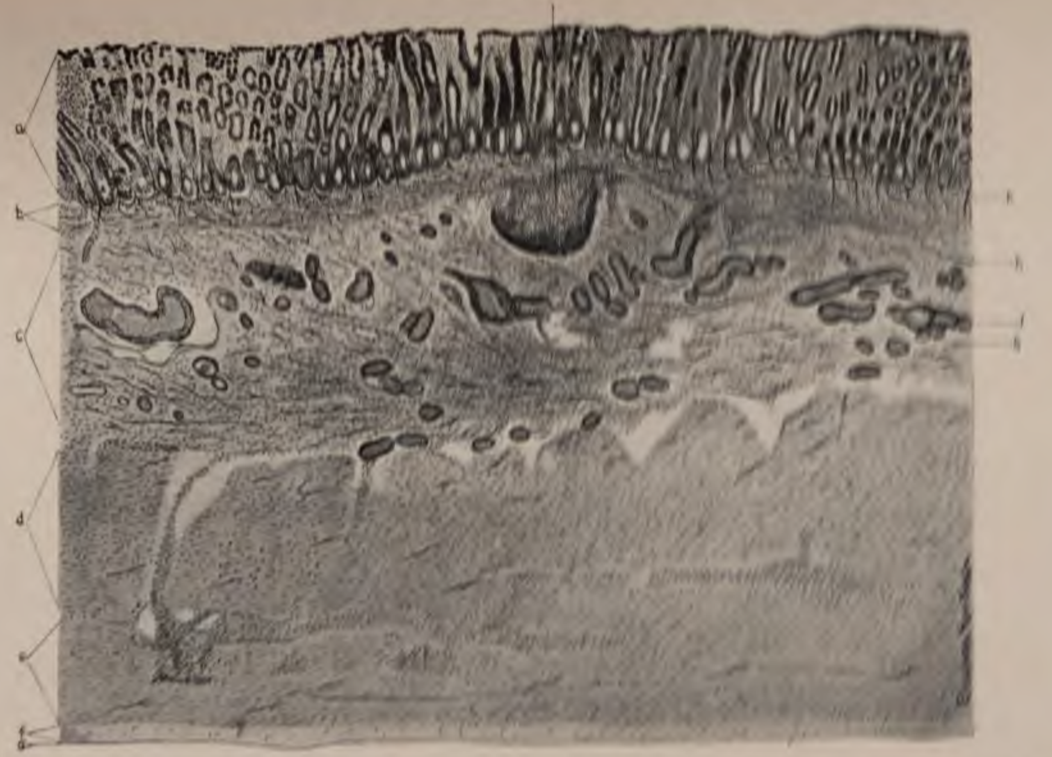
to the small intestine only a short distance behind the liver; it would thus appear that the greater part of the viscus might not inappropriately be styled the rectum—using the word in its generic sense. Its length and breadth vary, depending upon the size of the animal in which it occurs, but in the average dog it is 25 to 30 cm. in length. Its circumference also varies, depending upon the size of the animal and upon whether or not its muscular walls are in a state of contraction; in an ordinary dog this measurement will perhaps average from 5 to 7 cm. The intestine is attached to the upper portion of the wall of the abdomen by a mesocolon which very closely resembles that found in man. The wall of the bowel varies considerably in thickness, this again depending upon the size of the animal and also upon the state of contraction of its muscular layers; when in a relaxed condition and when normal it is, as a rule, about 3 mm. in thickness; but if it be contracted, or in a diseased state, this measurement may be doubled. The mucosa of the normal intestine is soft and velvety and of a pinkish-gray color; its surface is not, as a rule, smooth, the mucosa presenting numerous elevations and depressions, the number and size of which entirely depend upon the state of contraction of the muscular layers. These elevations, or rugæ, especially in the upper portion of the bowel, are occasionally longitudinal with its course, but in the lower half of the gut, particularly when the viscus is inflamed, they are almost always nearly or quite transverse to its long axis.

Examination with a low power shows the wall of the bowel to be divided into layers quite similar to those found in the intestine of man. These consist of a *mucosa*, a *muscularis mucosæ*, a *submucosa*, a *circular* and a *longitudinal muscular layer*, a *subserous coat*, and a *serous coat*, a detailed description of which now follows:

The *mucosa* has in the adult dog a thickness of about 1 mm. When examined under the microscope this coat is not uncommonly found covered with a thin layer of mucus, in which there are usually particles of undigested food, fragments of desquamated epithelial cells and bacteria; this layer varies very much in thickness, sometimes being entirely absent. Covering the surface of the mucosa there is a single layer of epithelial cells; these cells vary in height from 14 to 20μ, with an average of about 18μ. They vary exceedingly in width and are very irregular in form. In instances where they contain mucin they are commonly barrel-shaped, while the cells lying in the vicinity are constricted in the middle, thus resembling in their form the spools upon which thread is wound; not uncommonly they are columnar in form, while in other instances they are wedge-shaped. It is thus apparent that it would be impossible to state with any degree of accuracy their average width, and even the same cell always varies in this measurement in its different parts. The largest of all these cells are those that contain mucin, the width of which is sometimes as much as 20μ. Near the basal portion of the cells there is always a single vesicular nucleus, which may be rounded, oval in form, or spindle-shaped; the nucleus is surrounded by a distinct nuclear membrane, on the inner edge of which there are from five to eight minute masses of chromatin that vary considerably in size, and in the central portions of these nuclei a nucleolus is usually encountered. These nuclei vary in diameter from 4 to 8μ. The protoplasm of the cells is finely granular and stains with acid dyes. Mucin formation is very commonly observed in these cells; in the beginning the protoplasm of the cell becomes paler just above the nucleus, and on staining with the proper dyes this region is found to contain mucin. If specimens be stained lightly with Mayer's muchæmatein, or by the toluidin-blue picric acid method, there are found within these areas small, rounded, oblong or irregularly shaped masses which take the stain much more deeply than the surrounding mucin, and under these circumstances investigation will not uncommonly reveal a mucinoblast lying flattened out over the basement membrane to which the cell is attached. These masses resemble very greatly in form and in their staining reactions the granules encountered within the mucinoblasts. In a number of instances close investigation revealed the presence of granules lying in the protoplasm of the cells, between the mucinoblasts and the area containing mucin; it would thus appear that they have penetrated the basement membrane and have passed into the protoplasm of the mucin-bearing cells. The suggestion is therefore made that the mucin as it is found in the epithelial cells may have its origin, in part, in the granules that are contained within the mucinoblasts, and that these pass through the basement membrane upon which the epithelial cells lie, penetrate the protoplasm of the cells, and there, probably becoming united with some of the cellular constituents, produce what we call mucin. As the mucin-bearing cell increases in size these small masses become more numerous, and there appears to be little doubt—whatever their origin may be—that they exercise an important function in the production of mucin. As the mucin forms the cells increase in size, and, while they not uncommonly become somewhat longer, the enlargement occurs to a much greater extent in a lateral direction, with the result that they ultimately become rounded in form. Under these circumstances the protoplasm of the cell seems almost entirely to disappear, and the nucleus, reduced much in size and compressed into a crescentic form, lies between the masses of mucin and some part of the basal wall of the cell. The outline of the cell under these circumstances is by no means distinct, and the writer has in no instance been able to definitely determine whether the mucin remains confined to the original cell in which it begins, or whether it bursts into the surrounding cells; although this view would appear not impossible, it seems probable that this does not happen, for the reason that the mass of mucin would scarcely, under these circumstances, assume a rounded form and that there would be distinctly present beneath the masses more than one nucleus, which the writer has never been able to observe. In properly stained specimens the mucin may be frequently found in the act of discharging itself into the lumen of the intestine, but the writer has never been able to determine the subsequent fate of the remaining portion of the cells under these circumstances.

The surface of the intestine is beset with countless numbers of minute depressions which are the openings of those long, cup-shaped glands known as the *crypts of Lieberkuehn.* These structures are of two kinds—the *surface crypts* and those that, from their situation, the writer has called *lymph node crypts;* the latter correspond to the lacuna that have been described in the small intestines of some of the lower animals. The epithelial cells covering the surface of the intestine become continuous with those that line these glands, to which they are in almost every way similar.

PLATE I.



Section from about the middle portion of the large intestine of a dog. Specimen fixed in Bensley's solution. The drawing is a composite one, having been made from a section stained with hemalum, muchematein, and picric acid, and another stained with elashematein. Beck ⅙ inch, Oc. 1 inch *a.* Mucosa. *b.* Muscularis mucosæ. *c.* Submucosa. *d.* Circular muscular layer. *e.* Longitudinal muscular layer. *f.* Subserous coat. *g.* Serous coat, showing elastic tissue basement membrane. *h.* Bands of elastic tissue. *i.* Lymph node. *j.* Bloodvessels, in the walls of which there is much elastic tissue.

The *surface crypts* are almost as long as the mucosa is deep, there being between their bases and the muscularis mucosæ a distance of only about 30μ; from basement membrane to basement membrane they vary from 60 to 75μ in diameter, with an average of perhaps about 65μ. They may be divided into four portions—a *mouth*, a *neck*, a *body*, and a *base*.

Where the crypt opens upon the surface of the intestine there is a funnel-shaped depression—the *mouth* of the crypt. In this situation the epithelial cells lining the parts present peculiarities similar to those that characterize the surface layer of cells, with the exception only that mucin formation goes on here to a somewhat greater degree.

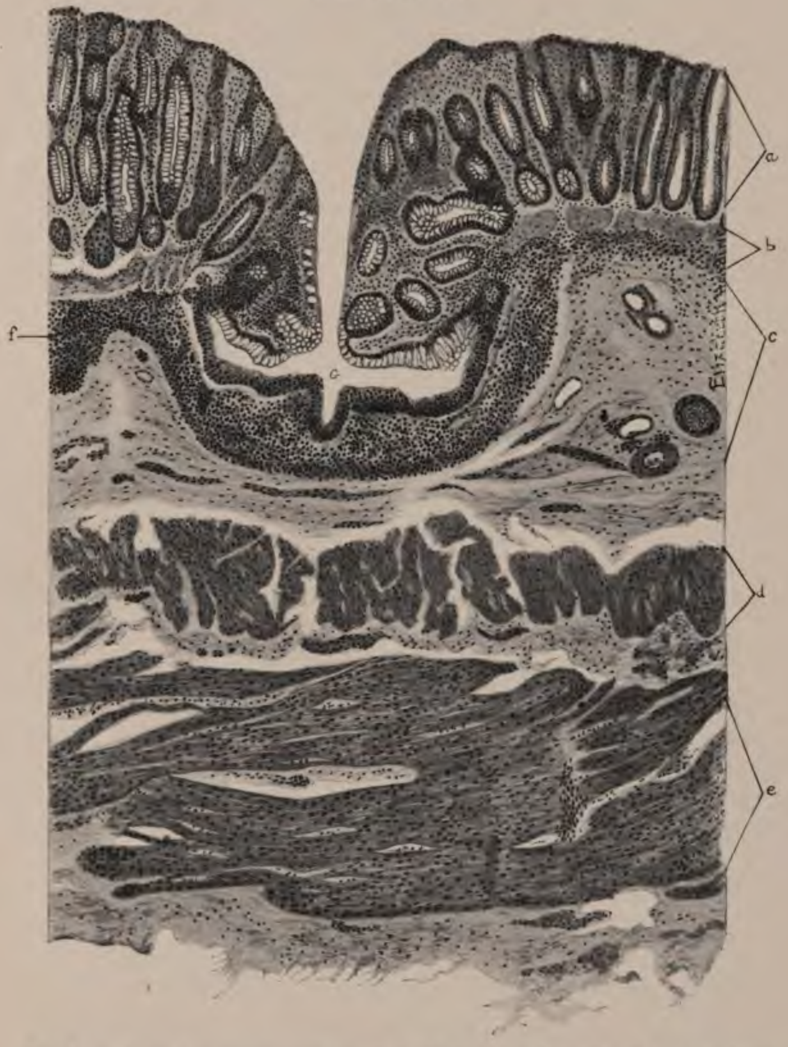
Immediately beneath the mouth of the crypt, and continuous with it, is the *neck* of the gland. Here the epithelial cells suddenly become considerably longer, this being in a large measure the result of the presence of great numbers of mucin-bearing cells. As a result of this the lumen of the crypt is suddenly greatly decreased in diameter.

Beneath the neck of the gland comes its *body*, which comprises practically the entire lower two-thirds of the crypt. In the upper portion of the body of the gland the epithelial cells are in every way similar to those found in the necks of the glands, but as the basal portion of the structure is approached they gradually become shorter as a result of the fact that mucin formation occurs with less and less frequency.

At the base of the crypt the epithelial cells become even shorter still, and, as a rule, the lumen of the crypt rather abruptly enlarges, it being here from 30 to 35μ in diameter. The epithelial cells in this situation are generally from 12 to 18μ in height, and the basal portion of their protoplasm contains multitudes of minute basophilic granules, causing them to appear when stained much darker than the cells higher up. These granules contain iron; it is highly probable that they are closely associated with the production of some substance that assists in the process of digestion, as they are nearly related to the prozymogen granules described by Bensley in the cells of the gastric tubules, and by Macullum in those of the pancreas. It is further true that mucin formation very rarely occurs in these cells in health.

In addition to the minute openings on the surface constituting the mouths of the surface crypts there are here and there found larger and much deeper depressions, these being the channels that communicate with the *lymph node crypts*. On examination it is found that the entire mucosa dips downward into the submucosa in these situations, and that that part of the mucosa that lies at a lower level than the muscularis mucosæ is entirely surrounded by masses of lymphoid tissue. The glands that open around the edges of the mouths of the lymph node crypts resemble in every way those present in other situations, but just at the bottom of the crater-like depression there are always found one or more crypts that differ somewhat from those higher up. These glands are characterized by the fact that from the bottom of the large opening there radiate at right angles numerous primary glands, and these in some instances give off branches. These glands are further peculiar in that they are very large, some of them being from basement membrane to basement membrane as much as 140μ in diameter. The cells lining the openings leading into these crypts resemble in every way those that are found in the necks of the surface glands, and, like them, oftentimes contain mucin, —this peculiarity, curiously enough, being particularly prominent on the sides of the ducts toward the free surface of the intestine. The mucin-bearing cells in these situations are the tallest epithelial cells found in the large intestine of the dog, they being commonly from 40 to 50μ in height. In the deeper portion of these crypts the epithelial cells resemble in every particular those found in the bases of the surface glands, with the exception only that they are generally considerably larger, usually measuring from 25 to 30μ in height. These cells do not lie on a basement membrane, but seem to be in direct contact with the lymphoid cells that are immediately beneath them; this peculiarity of the cells in these situations has been noted in the intestines of other animals by Davidoff, and this portion of the gland was called by him the *intermediary zone*. The epithelial cells lining the deeper portions of these glands, as well as those occurring in like situations in the surface crypts, often contain mitoses; they are easily found, for the reason that nuclei undergoing this change lie more superficially than those in the resting stage.

PLATE II.



Specimen from the upper portion of the large intestine of a dog. Specimen fixed in Bensley's solution and stained with hæmalum and eosin. Beck ¼ inch, Oc. 1 inch. *a.* Mucosa. *b.* Muscularis mucosæ. *c.* Submucosa. *d.* Circular muscular layer. *e.* Longitudinal muscular layer. *f.* Lymph node. *g.* Lymph node gland.

The cells lining the crypts of Lieberkuehn lie upon a delicate basement membrane which is thickest around the basal portion of the glands, and becomes at the mouths of the crypts, and beneath the epithelium lining the superficial surface of the mucosa, exceedingly thin. Around the bodies and bases of the glands this membrane has an average thickness of about 2μ, but beneath the surface epithelium it generally measures something less than 1μ in thickness. It is very interesting to note that this membrane reacts in a perfectly characteristic manner to the elastic tissue stain of Weigert, and to the hæmatein elastin stain described in Part I.

Between the crypts there is always a certain amount of interglandular substance, varying in thickness from 5 to 15μ. This contains a delicate network of fibrils of what appears to be collagenous tissue, since they react perfectly to the stains that exhibit most affinity for this substance. These fibres commonly measure something less than 1μ in thickness. Lying in the lymph spaces between the collagenous tissue network there are always found quite a number of lymphoid cells, an occasional polymorphonuclear leucocyte, quite a number of mucinoblasts, and, in addition, especially around the bases of the glands, there are commonly present cells that have the shape of and stain very much like plasma cells. The mucinoblasts commonly lie in contact with the basement membranes of the crypts, upon which they seem to be flattened out; reference has already been made to the fact that the granules found in these cells appear in some instances to permeate the basement membranes and to penetrate the mucin-bearing epithelial cells. The cells above mentioned that so closely resemble plasma cells differ from them only in that the granules that they contain are, as a rule, not altogether so large and do not take the basic stain with precisely the same degree of intensity as the granules found in these cells. Minute capillaries are frequently found in the interglandular tissues. The structures that lie between the bases of the crypts and the muscularis mucosæ resemble those occurring between the glands in every particular, with the exception only that the pseudoplasma cells are more commonly present, and that there pass up through it many fibrils of elastic tissue from the muscularis mucosæ. These bands of elastin become united to the outer portions of the basement membrane of the crypts at the points where these structures pass upward to surround the bodies of the glands, and they are of great importance, as they afford the only real attachment of any strength that binds the mucosa to the layers underneath.

The *muscularis mucosæ* is composed of two parts—an inner circular and an outer longitudinal muscular layer. In some situations the outer longitudinal layer becomes exceedingly thin, and may for a short distance entirely disappear. In those areas where the lymph node crypts exist the entire muscularis mucosæ is interrupted, no vestige of it being found in the surrounding tissues. The muscularis varies considerably in thickness, but the two coats together are perhaps, on an average, of about 75μ in thickness. It is very curiously the case that the longitudinal layer in those situations where it occurs is usually somewhat thicker than the more constant inner circular layer, the former measuring usually about 45μ and the latter 30μ in thickness. These layers are largely made up of ordinary unstriped muscle fibres which contain about their central portions spindle-shaped nuclei. It was impossible to measure the length of these fibres with any accuracy in sections, and for this reason no attempt will be made to give their dimensions further than to say that they appear to be about the usual size of unstriped muscular fibres.

Between the muscular tissue there is a delicate network of elastic tissue, the fibrils measuring from 1 to 2μ in thickness. These fibres become continuous with those that pass up through the tissues lying beneath the bases of the crypts, and, as before stated, ultimately attach themselves to the outer portions of the basement membranes that surround the bodies of the glands.

Beneath the muscularis mucosæ, and separating it from the circular muscular layer, is the *submucosa.* This coat has an average thickness of perhaps 0.5 mm., but it varies considerably in this measurement. The coat is always much thicker immediately beneath those elevations on the mucous surface that have been described in speaking of the anatomy of the intestine, but it is highly probable that these rugæ are never constant in any one situation, and that the increased thickness of the submucosa is only of a temporary nature. These puckerings of the submucosa are unquestionably due to contractions of the muscularis mucosæ. The submucosa is made up almost entirely of collagenous tissue, mixed with which there is more or less elastin; although the fibrils composing these tissues run, for the most part, in a circular manner, many of them run longitudinally and some obliquely. Lying within the tissues there are quite a number of fixed connective tissue cells and many mucinoblasts; in addition to these an occasional lymphoid cell or polymorphonuclear leucocyte may be found. Scattered all through the tissues there are numerous bloodvessels. The submucosa of the large intestine of the dog is particularly rich in lymph nodes, these being in some cases so small that they do not occupy more than one-fifth or one-sixth of the thickness of the gut, while in other instances they replace the tissues completely from the circular muscular coat to the surface epithelium that covers the mucosa. In the larger nodes there are frequently present those peculiar lymph node crypts, a description of which has already been given. These lymph nodes are made up of lymphoid cells almost entirely, but there are not uncommonly in addition a few pseudoplasma cells, and an occasional mucinoblast. No lymphatics penetrate these structures, but there are always a number of vessels of this kind surrounding the nodes. This coat also contains nerve plexuses, in which there are medullated and non-medullated nerve fibres and likewise ganglion cells.

Immediately external to the submucosa is the *circular muscular layer*, to which it is united by numerous prolongations of the former that pass down between the bands of muscle fibres, forming the intermuscular septa. The thickness of this layer varies somewhat, depending upon the state of contraction of the fibres composing it, but in general it is from 1 to 1.25 mm. in thickness. In addition to the intermuscular septa just referred to, the coat is made up of unstriped muscle fibres that correspond in every way to those referred to as occurring in the muscularis mucosæ. Between the muscle fibres everywhere there is a delicate network of elastic tissue. This network is composed of comparatively coarse fibres that radiate from the intermuscular septa; the fibrils measure from 0.5 to 1μ in thickness. These structures stain intensely with the specific stains for elastic tissue, and there can be no question of their true nature. Radiating from these large bands there are multitudes of minute fibres, having a diameter of from 0.3 to 0.4μ, that lie between each individual muscle fibre and act as sheaths for them. It should be noted that elastic tissue is very abundant in the intermuscular septa. In the lymph spaces of the muscular layers there are generally present quite a number of mucinoblasts and lymphoid cells, and polymorphonuclear leucocytes are occasionally encountered.

External to the circular muscular layer is the *longitudinal muscular layer;* this coat is united to the circular muscular layer by means of bands of collagenous and elastic tissue, each being present in about equal quantity. The longitudinal muscular layer is somewhat thinner than the circular muscular layer; but in some situations, as, for example, at the point where the mesocolon is attached, this layer even becomes much thicker. The histology of this coat corresponds in every way to that of the circular muscular layer.

External to the longitudinal muscular layer there is a thin coat composed of a loose network of fibrous and elastic tissue that is very variable in thickness and in its component parts; this is the *subserous layer.* It contains, in addition to bloodvessels, nerves, and lymphatics, quite an amount of fat where the mesocolon is attached. There are occasionally found in its tissues a few connective tissue cells and an occasional lymphoid cell or polymorphonuclear leucocyte.

At all points, except where the mesocolon is attached, the subserous coat is covered by a *serous layer.* This is made up of delicate basement membrane that gives an intense stain-reaction to the specific stains for elastic tissue. The membrane is covered on its external surface by pavement epithelium, upon the free surface of which, in properly prepared sections, minute ciliæ may be demonstrated.

PART III.

EXPERIMENTAL DYSENTERY IN DOGS.

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NUMEROUS attempts have been made by the writer to experimentally induce changes in the intestines of dogs by the rectal injection of various bacteria and fecal matter from individuals suffering from dysentery. Among the organisms experimented with are the so-called typhoid bacilli, colon bacilli, the ray-fungi, anthrax bacilli, the staphylococci and streptococci of suppuration, the mixed bacteria that were grown from the feces of individuals suffering with dysentery, and the so-called bacillus dysenteriæ of Shiga. As a general rule, several dogs have been experimented upon with each of the organisms mentioned; in a number of cases they were quite young, and therefore presumably somewhat more susceptible than older animals. In order to prevent the injected material from being at once expelled, in almost every instance the dogs received morphine hypodermatically an hour or so before the bacteria were introduced into their intestines, and there can be no doubt that in practically all cases the micro-organisms were retained in sufficient quantity to furnish a reasonable test of their pathogenic power. Bouillon cultures of the bacteria were in most instances used for the experiments, though in some cases the organisms were removed in mass from solid media and thoroughly ground up with sterilized water in a mortar before being injected. As a general rule, 10 c.c. of the bouillon cultures were administered, but in some cases the amount was greater and in some less. A record of the time, the quantity of bacteria injected, and the sizes of the dogs experimented upon was carefully kept in every instance, and the subsequent histories of the animals were likewise preserved. A study of these records shows that not in a single instance did a dog exhibit evidences of disease following the injection of bacteria, and in most cases they were entirely healthy for weeks and even months thereafter. These results are of much interest, particularly as regards the organism supposed to be the cause of the acute dysentery of the East—the bacillus first described by Shiga. The cultures used were obtained from Prof. Simon Flexner, of the University of Pennsylvania, to whom the writer desires to express his thanks. It seems significant that these organisms entirely failed to produce any effect on four ten-day-old puppies, into the large intestines of which they were injected, nor did any disturbance follow when they were introduced into the large intestines of three cats.

Much more satisfactory were the results obtained by injecting fresh feces of individuals suffering with dysentery into the large intestines of puppies, for in every case in which this was done a typical dysentery immediately developed that resulted in the death of the animals, except in one instance where the dog was killed. It should, however, be stated that no ill effects followed the injection of material of this kind into the large intestines of four adult dogs and in three cats that were almost grown. It would thus seem that puppies are particularly susceptible to the disease-producing cause of this variety of dysentery. These are not the first successful experiments of this kind, for Hlava[1] induced dysentery in two dogs out of seventeen injected with dysenteric material, and in four cats out of six that had been subjected to a like treatment. Kartulis[2] succeeded in producing dysentery in three cats out of seven, he having injected the stools from patients suffering with dysentery, and also cultures of the amœbæ.

Numerous attempts were made to cultivate the amœbæ, but in no instance were they successful; it was therefore impossible to determine what the result would be should these micro-organisms be introduced in this state into the intestines of animals; but the experiments of Kartulis, already referred to, indicate that the pathogenic agency exists in cultures containing amœbæ made from the discharges of patients suffering with dysentery, and he even asserts that the disease was produced in a cat as a result of the introduction of these organisms in a pure form into its intestine. There seems, however, some tendency among writers to doubt the correctness of his statements concerning the latter experiment, for the reason that no one else has so far succeeded in obtaining these parasites in pure culture.

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[1] Centralbl. f. Bak., Band i., 1887.

[2] Eineges über die Pathogenes der Dysenteriaemoeben, Centralbl. f. Bak., ix., 1901.

Since it was impossible to cultivate the amœbæ, it occurred to the writer that the next best thing would be to attempt to cultivate all of the bacteria in the discharges of dysenteric patients, and to determine if these mixed cultures were capable of setting up a dysenteric process. Cultures were accordingly made from the feces of the same individuals whose discharges had been used to successfully produce dysentery, and these were then injected into the intestines of four puppies. There was absolutely no effect produced. It therefore seems unreasonable to conclude that the germ that produces the disease is a bacterium, or, at any rate, it seems fairly certain that it cannot be an organism that develops or even lives in the culture media ordinarily employed. As neither of these suppositions appear at all probable, and as the amœba coli was the only other living organism found in the feces that was probably absent from the cultures, it seems logical to suppose that this parasite is the cause of any morbid state that the injection of these discharges may give rise to. As will be seen further on, this view is supported by the fact that the amœbæ are abundantly present in and around the ulcers that are found in the intestines of the dogs suffering with experimental dysentery, and it does not appear unreasonable to say that the proof is now fairly clear that these organisms are in reality the causative agents in chronic dysentery.

Dysentery in Dogs Resulting from the Injection of the Discharges of Individuals Suffering from Dysentery.

EXPERIMENT I. Duration, about four days.

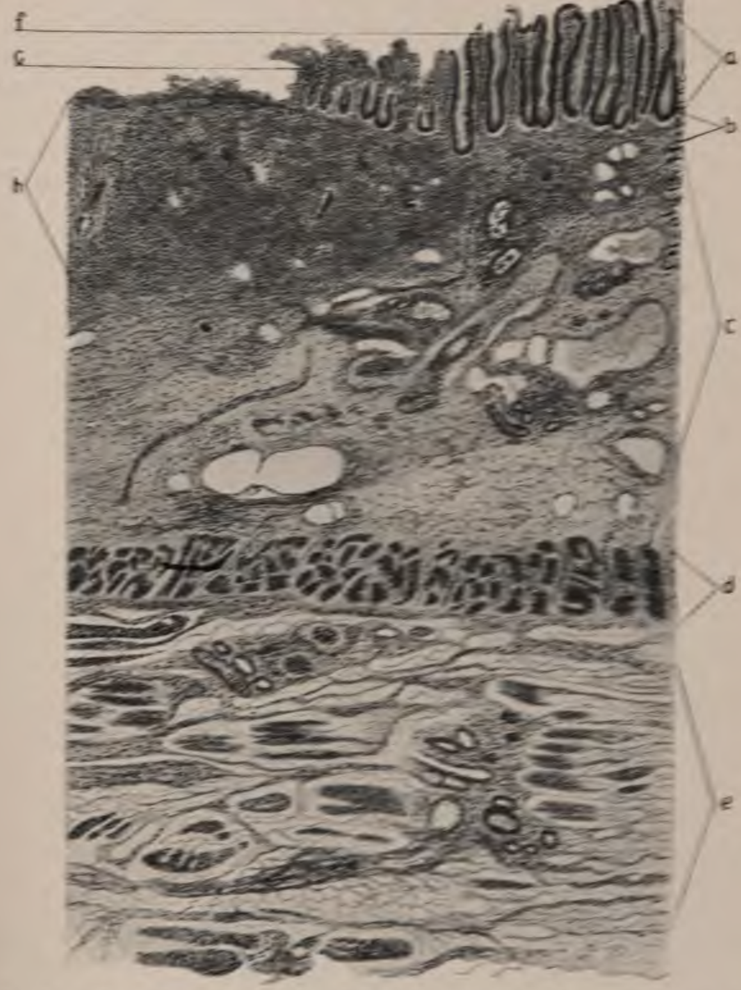
On December 7, 1900, at 5 P. M., about 0.5 c.c. of fresh fecal matter, from a negro woman suffering with dysentery, was injected into the large intestine of a puppy three days old. Some of the fecal matter examined immediately before the injection was given showed that it was made up very largely of mucus, mixed with blood, in which there were many bacteria and a large number of living amœbæ. The animal was not examined until four days later, when there was found quite a quantity of slightly blood-stained mucus around the anus and in its immediate neighborhood. Two of the puppies of the same litter that had been simultaneously injected with the dysenteric material also showed blood-stained mucus around their anuses, but five others that had not been injected presented no evidence of the disease. Some of the mucus from each of the puppies was immediately submitted to microscopic examination, and in every instance found to contain many active amœbæ, numerous blood cells, and a great number of bacteria.

The puppy first referred to was killed and a post-mortem was at once made. About one-fourth of the large intestine, from the anus upward, was greatly swollen; its mucous surface appeared rough and uneven, and was of a grayish color, with here and there minute pinkish spots upon it. On close inspection it was evident that the irregularities just referred to were the result of superficial necrosis of the mucous membrane, and that shallow ulcers had already begun to form on the surface of the intestine.

Sections of the large intestine were prepared for microscopic examination, and showed in an unmistakable manner, when examined by the unaided eye, that the affected regions were greatly swollen. On microscopic examination with a low power very extensive ulceration was at once apparent in the diseased areas; these ulcers are always situated on the apices of the rugæ. Overlying the affected regions there are invariably found masses of granular débris containing mucus, blood, disintegrated and disintegrating cells, numerous bacteria, and many amœbæ; small collections of fibrin are occasionally present in this granular material. In the central portions of the areas that are most swollen the ulcerative changes have usually progressed to such an extent that the greater part of the mucosa has entirely sloughed away, and in many instances ulceration completely through this coat, and even down into the submucosa, is found. In the edges of the parts of the mucosa most affected there are numerous minute areas in which the ulcerative change is just beginning and in which its course and development may be traced with the utmost clearness. The process begins as a catarrhal change in the epithelial cells that line the surface of the intestine; these cells first swell up, become irregular in form, quite granular, their nuclei take the basic stain feebly, and the protoplasm becomes abnormally acidophilic. Following this the cells quickly fall off and disintegrate. The basement membranes upon which they lie next give way, and the tissues between the glands are in this way directly exposed and brought in contact with the contents of the gut. Simultaneously with the shedding off of the epithelial cells the lymph spaces that lie in the tissue beneath become enormously enlarged and filled with fluids, and, the bloodvessels also dilating, the tissues are greatly swollen as a result. It quite commonly happens that some of the distended bloodvessels burst, and in this way red blood cells are found numerously present within the tissues, and as soon as the basement membrane gives way quantities of blood pass out and become mixed with the mucus and other contents of the bowel. Following this, numerous cellular elements collect in the swollen tissues, these consisting, in the early stages, of lymphoid cells and large phagocytes of Metschnikoff (epithelioid cells), mixed with which there are a few connective tissue cells and plasma cells. These alterations extend downward between the crypts; ulceration of the affected tissues rapidly ensues, and in a short time, the glands no longer having support, drop out and become intermingled with the granular débris that lies on the surface of the gut. When this stage is reached the lumina of the crypts are always much diminished in size, owing to the pressure produced by the collections of cells and fluids in the intervening tissues. Even under these conditions the cells that line the crypts show remarkably little change, as the glands are often preserved practically intact when completely surrounded by masses of necrotic material; the cells lining the crypts, however, appear somewhat swollen, their nuclei are larger than normal, and mitotic figures are scarcely ever observed. A more marked alteration than any of these just referred to consists in the fact that the cells have apparently in a large measure ceased to secrete mucin, this substance never appearing as the small, oval masses seen in the normal glands, but when it occurs at all is present rather diffusely within the protoplasm of the cells. In some instances, after the crypts have sloughed completely away from the mucosa and the basement membranes and surrounding tissues have been destroyed, the cells appear in small, irregular collections, but still preserve to a great degree the peculiarities that they exhibit in a normal condition. Lying upon the surface of these newly affected areas, and sometimes in the tissues a short distance from the surface, amœbæ are invariably found; although in a microscopic section only a few of them, as a rule, are present, the number in the affected portion of the mucosa must be considerable. As has just been stated, the amœbæ may be present only upon the surface of the tissues and not lying within them; from this it must be admitted that if they be the real causative agents in this disease they undoubtedly act by means of some toxin produced, and not at all, as one would be inclined to suppose, in a mechanical way.

Where the changes have gone on more extensively the mucosa has in some instances entirely sloughed away, and, more rarely, the ulcerative process has extended even into the submucosa. Under these circumstances there are always found over the surface of the diseased tissues—even in greater amount than over the recent ulcers—masses of granular material containing degenerating cells of all kinds, mucus, many bacteria, and numerous amœbæ. The tissues constituting the surfaces of these ulcers consist almost wholly of cells, the muscular and elastic tissues of the upper part of the submucosa having entirely disappeared, owing to the enormous cellular accumulations in the parts. It is noteworthy, however, that the muscular tissues of the muscularis mucosæ so far preserve their integrity in many instances as to be still distinguishable, while the underlying structures of the submucosa have practically disappeared. These cellular accumulations consist of quite a number of polymorphonuclear leucocytes, many lymphoid cells, a few plasma cells, an occasional mucinoblast, numerous red blood cells, and enormous numbers of the large phagocytes of Metschnikoff (epithelioid cells). In the upper part of this layer amœbæ are frequently found intermixed with the cells just described, and a few bacteria are also some-

PLATE III.



Specimen from the lower portion of the large intestine of a puppy, into the rectum of which a small amount of fecal material containing living amebæ had been injected four days previously. The tissues were fixed in Bensley's solution and stained with hemalum and eosin. Beck ⅙ inch, Oc. 1 inch. *a.* Mucosa, which is entirely absent on the left side of the drawing. *b.* Muscularis mucosæ, the tissues of which show great alteration beneath the point where the mucosa is absent. *c.* Submucosa, which is swollen and contains beneath the ulcerated area multitudes of large phagocytes, many polymorphonuclear leucocytes, a few lymphoid cells, plasma cells, mucinoblasts, and amebæ (*h*). *d.* Circular muscular layer. *e.* Longitudinal muscular layer. *f.* Beginning necrosis of the surface epithelium at edge of ulcer. *g.* Cellular collection replacing mucosa at the margin of the floor of the lesion. (Exp. 1.)

times present. Mucinoblasts, as above stated, are found in the diseased tissues, but their number is somewhat less than in the normal parts of the intestine. On either side of these areas, and downward more deeply in the submucosa, the cells gradually diminish in number, and give way to the normal tissues of the part. In those situations where the ulceration extends beneath the muscularis mucosæ there are found intermingled with the cells the remains of the original connective tissues of the parts. The elastic tissues have apparently disappeared, for no structures are present that stain either by Weigert's method or by the hæmatein process described in the opening chapter of this essay. There are, however, a number of elongated, irregularly shaped masses in these situations that react feebly to the stains for white fibrous tissue, and which appear to be the degenerate remains of these structures; these masses are much thicker than are the fibres of collagenous tissue found in the submucosa, and around their edges they are almost universally exceedingly ragged and their margins are ill-defined. Quite often the connective tissues have evidently completely disintegrated, as there are found between the cells small granular masses that, from their forms, apparently represent these structures. Deeper down the elastic tissues are still no longer found, but many swollen fibrils of collagenous tissue are always present. As has been before remarked, the cells that are so numerously present at the surfaces of the ulcers and in their immediate vicinity gradually diminish deeper down in the tissues and to either side of the lesions, but even in situations so remote that none of these cells are present the elastic tissue stains very poorly, and the collagenous tissue fibrils are swollen here and there. In the tissues bordering on the ulcers the bloodvessels, especially the veins, are somewhat dilated, but the change is not so marked as one would be led to suppose from the nature of the lesions. The walls of the vessels very near the surfaces are swollen, the elastic tissue fibrils within their coats no longer take their specific stains, and the muscular fibres stain rather diffusely and no longer present the well-defined outlines that characterized them in health. These changes are always most marked on the sides of the vessels nearest the ulcers. A much more pronounced condition is the enormous dilatation of the lymphatics, and the presence within them of many red blood cells and leucocytes, and, in almost every instance, masses of desquamated epithelial cells that originally lined these channels. These desquamated epithelial cells are enormously enlarged; so much so that they are about the size of the cells lining the crypts. They are very irregular in form and are acidophilic throughout, though with strong basic dyes their nuclei can usually be distinguished. In some instances these cells are so numerously present that they completely block up the lymph channels. The submucosa is always swollen to quite a distance beyond the ulcers, and the greatly dilated lymph spaces in these regions generally contain numerous red blood cells. In no case have the changes extended beneath the submucosa, but in most instances the lymph spaces are dilated and contain numerous blood cells and a few lymphoid cells even down to the circular muscular layer.

EXPERIMENTS II. AND III. **Duration, fourteen and sixteen days, respectively.**

The two other puppies that had received injections of dysenteric material simultaneously with the one referred to in Experiment I. showed similar evidences of having contracted dysentery. Both developed diarrhœa two or three days after the injections were given, and a few days later the stools contained quantities of mucus and blood in which there were numerous living amœbæ. However, the animal that died in fourteen days did not exhibit such severe symptoms as the other, and, although considerably emaciated, had not lost so much flesh. The earlier death of this puppy is in keeping with the clinical history of the disease as it is observed in man, as it frequently happens that those apparently but little affected die before those who seem to have the malady in a much severer form. As soon as the puppy just referred to was found dead an autopsy was made, with the following results:

The large intestine was empty and its mucosa hyperæmic throughout. The mucous coat was apparently ulcerated away several inches above the anus, and many small ulcers were observed in the upper part of the gut, even up to the margin of the ileocæcal valve. The edges of these ulcers were raised slightly above the surrounding mucous surface, and in some situations appeared to be slightly undermined; their floors were of a grayish color.

A small abscess about 1 cm. in diameter was found in the substance of the liver just above the gall-bladder; the contents of this abscess were of a grayish color and contained numerous fragmented liver cells, quite a number of polymorphonuclear leucocytes, and a few amœbæ.

Sixteen days after the injection was given the remaining puppy was found in a dying condition. The animal was killed with chloroform and an autopsy was at once made. The puppy was greatly emaciated. On examination the large intestine was found to be empty. The wall of the gut was considerably thickened, and its mucous surface was of a pale pinkish-gray color. The entire mucosa was beset with great numbers of small ulcers—generally 2 mm. or 3 mm. in diameter—that in every way resembled those already described as occurring in the intestines of the other puppies. The ulcers were not more frequently present on the tops of the rugæ than elsewhere on the mucous surface, though it should be remarked that these elevations are not so numerous or well-marked as is usually the case.

The liver contained six small abscesses, the largest being about 0.5 cm. in diameter. These abscesses presented the appearance of those found in the liver of the other puppy.

As the microscopic lesions in the intestines of these two puppies are in every way similar, the description that follows applies to both:

On examination with low powers the mucosa is found to present extensive alterations; indeed, this coat of the intestine is in a large measure absent, there being only here and there small islets in which the normal tissues are more or less preserved. In situations where the changes are least marked mucin formation is going on in the lining cells of the crypts to an unusual extent—none of the cells under these circumstances being free from this substance—and, as is so often the case where the epithelial cells are subjected to irritating influences, the mucin does not occur in the small globular masses as in health, but scattered diffusely throughout the protoplasm of the cells.

In the interstitial tissues lying between the crypts the blood-

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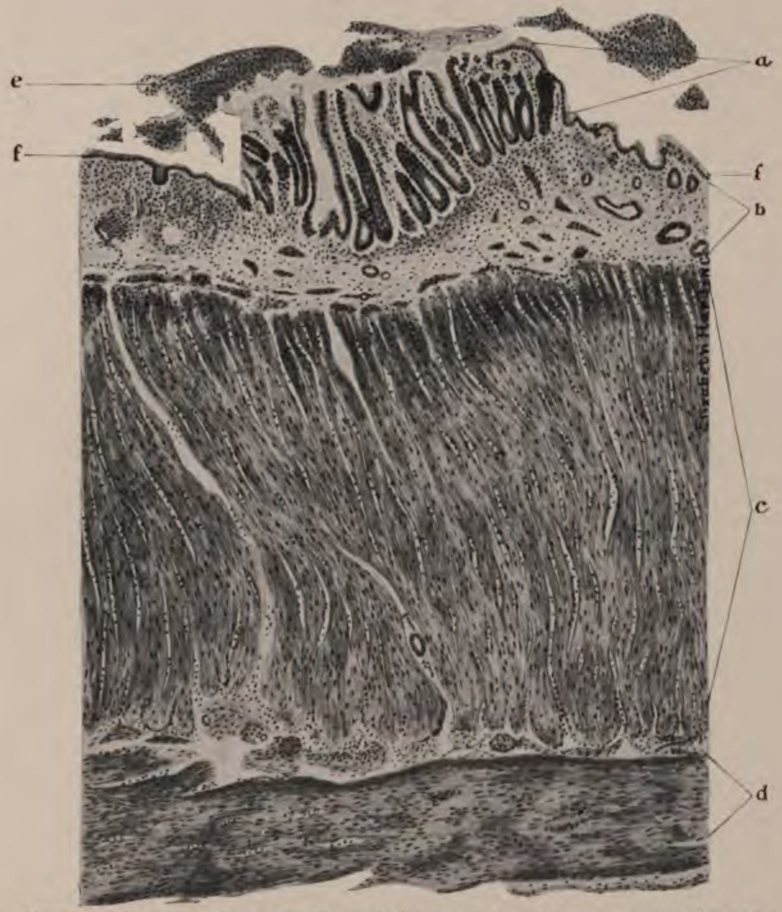
vessels are considerably dilated and are filled with blood, and the surrounding lymph spaces are distended, contain many blood cells and an unusual number of lymphoid and plasma cells; the effect of this, of course, is to cause this coat to be considerably swollen. Beneath these areas the muscularis mucosæ generally shows no apparent alteration, but the tissues of the submucosa are always swollen and contain a great many lymphoid cells, and many more than the usual number of mucinoblasts, a quantity of plasma cells, and a very few polymorphonuclear leucocytes. The epithelial cells lining the bloodvessels and lymph spaces are also considerably swollen, as a rule, and not infrequently have shed off from their basement membranes.

At the edges of the areas least affected there are found two distinct classes of lesions, though they at many points merge insensibly into each other. One of these represents recent changes in the mucosa and the other the lesions of a more chronic kind. The former will be first considered.

No extended description of the more recent lesions is necessary, for in those instances where the necrotic process has just begun, or has not been in existence for a great length of time, changes are found that in every way resemble those encountered in the beginning ulcers described in connection with Experiment I.

In the more chronic ulcers the necrotic process has passed through the mucosa in all instances, and extends to a varying distance into the submucosa; in some cases the entire submucosa has sloughed away, but under no circumstances have even the superficial portions of the circular muscular layer undergone ulcerative change. The tissues forming the floors of these lesions, as a rule, are made up of necrotic connective tissue, but in some instances a remarkable development of epithelium has occurred over the exposed surfaces of the ulcers, and in some cases has completely covered them. This layer of epithelium is attached to the tissues that lie beneath, and follows closely the irregularities of its surface; in many instances the cells have grown downward into the tissues, lining what were apparently enlarged lymph spaces, and forming glandular structures that greatly resemble the normal crypts. These newly-formed crypt-like bodies have their bases sometimes on the circular muscular

PLATE IV.



Specimen from the lower portion of the large intestine of a puppy, into the rectum of which a small amount of dysenteric material containing living amœbæ was injected fourteen days before the death of the animal. The tissues were fixed in Bensley's solution and stained by Benda's iron-hæmatoxylin method. Beck ¼ inch, Oc. 1 inch. *a.* Mucosa, which is absent at either side of the drawing. *b.* Submucosa, containing many lymphoid cells, numerous plasma cells, and quite a number of mucinoblasts; there is much newly-formed fibrous tissue in this layer. *c.* Circular muscular layer. *d.* Longitudinal muscular layer. *e.* Granular débris on surface of the intestine. *f.* Layer of newly-formed epithelium. (Exp. II.)

coat, and not infrequently extend out laterally for quite a distance into the submucosa. The cells constituting this newly-formed epithelial covering of the ulcers, and those found in the newly-formed crypt-like bodies, resemble very greatly the normal epithelial cells on the free surfaces of the intestine. They occur in a single layer, and consist of tall, well-defined, columnar epithelial cells, the nuclei and protoplasm of which stain in the usual way, but under no circumstances does mucin formation appear to go on within them. Mitotic figures are never observed in these cells.

The tissues lying beneath these ulcers consist of numerous very dense bodies of white fibrous tissue and quite a number of fibrils of elastic tissue. The white fibrous tissue has evidently increased in amount, as it is present in considerably greater quantity than is found in the normal submucosa. The lymph spaces in these situations contain very little fluid and never appear unusually dilated. Scattered throughout the tissues there are great numbers of lymphoid cells, many plasma cells, and a very unusual number of mucinoblasts; there are also a few more or less degenerate connective tissue cells and an occasional polymorphonuclear leucocyte. The bloodvessels are not particularly numerous and never appear dilated in these areas; it may be noted, however, that the epithelial cells lining the bloodvessels and the larger lymph channel generally appear swollen, and, especially in the latter, have oftentimes shed off from their basement membranes. Fibrin is never found in these tissues, nor have bacteria been demonstrated in any of the specimens examined.

The circular muscular layer shows no alteration further than that there is an unusual number of mucinoblasts lying between the muscle fibres.

The longitudinal muscular layer and subserous and serous coats appear entirely normal.

From the foregoing description of the changes that occur in experimental dysentery in dogs it will be seen that the lymph nodes of the intestinal wall show no peculiar or striking alterations in this disease, and, indeed, it may be said that these structures are always, as it were, incidentally affected, and that they never show alterations of a more pronounced kind than are seen in the neighboring tissues.

It will be recalled that abscesses were present in the livers of both of the puppies.

On microscopic examination it was found that the contents of these abscesses consisted of degenerate liver cells, considerable numbers of polymorphonuclear leucocytes, and, in some situations, degenerated red blood cells. The necrotic liver cells frequently formed long, irregular rods, rounded at the ends, that greatly resembled those masses that result from the breaking up of hepatic cells in the liver of man under similar conditions. In properly stained sections a few bacilli may be demonstrated, and a small number of amœbæ are here and there found. These abscesses were evidently recent, for their walls consist merely of compressed liver cells that are more or less necrotic. The hepatic cells in the vicinity of the abscesses show evidences of beginning degeneration, but there is not that wide-spread and very marked necrosis of these cells that occurs in amœbic abscesses of the liver in man. The capillaries in the vicinity of the abscesses are filled with polymorphonuclear leucocytes, and, in many instances, apparently contain no red blood cells at all; further away the capillaries are distended with blood and are somewhat dilated, but these alterations are by no means marked.

EXPERIMENT IV. **Duration, sixteen days.**

A puppy, twenty-six days old, was injected with fecal material containing living amœbæ. In a few days the animal developed dysentery and died in sixteen days after the dysenteric material had been administered. Its intestine presented changes in every way similar to those found in Experiments II. and III.

Résumé of the Alterations found in the Large Intestines of Dogs Suffering with Experimental Dysentery.

On post-mortem examination the large intestines were in all cases found swollen and the mucosa somewhat reddened in the affected regions. There were scattered over the surface numerous small ulcers, these being limited to the lower part of the small intestine in the case where the animal was killed; but in those instances where death resulted from the disease these lesions were observed on all parts of the surface of the bowel. In two of the cases there were liver abscesses.

On microscopic examination considerable alterations are apparent in the intestinal walls. Where the lesions are only beginning there are merely slight catarrhal changes in the surface epithelium, in the immediate vicinity of which amœbæ are invariably found. At a later stage the epithelial cells entirely desquamate and their basement membranes disappear. Simultaneously the interglandular tissues beneath become greatly swollen as a result of the accumulation of liquids in the parts and of the dilatation of the bloodvessels; in many instances the walls of the vessels burst, and hemorrhage occurs in the parts. In addition to the pre-existing cells normally found in these situations great numbers of large phagocytes of Metschnikoff quickly collect. Following this, ulceration begins from above, and, extending downward between the glands, continues until these structures, no longer having support, drop out of the intestinal wall.

The muscularis mucosæ resists the process decidedly, but in many instances the tissues composing it have likewise become necrotic and have sloughed away; under these circumstances the ulcers extend into the tissues of the submucosa. It is, however, often the case that remnants of the muscularis mucosæ are found in situations where both the tissues above and below are entirely necrotic. The floors of these deeper ulcers consist of the remains of the pre-existing tissues of the parts, intermingled with which there are multitudes of the large phagocytes of Metschnikoff, many polymorphonuclear leucocytes, and a few lymphoid cells, plasma cells, and mucinoblasts. It is particularly noteworthy that while all of the connective tissues in these situations undergo rapid alteration, the elastin suffers more than the collagenous tissues and very quickly disappears.

In the more chronic lesions similar alterations are found, with the exception only that the large phagocytes have given way to great numbers of plasma cells, and that fibrous tissue is being formed in considerable quantities.

In no instance has the necrotic process extended into the circular muscular layer.

PART IV.

EXPERIMENTAL PRODUCTION OF CHANGES IN THE LARGE INTESTINES OF DOGS BY MEANS OF HEAT AND BY THE INJECTION INTO THEM OF VARIOUS IRRIGATING SUBSTANCES.

PART IV.

EXPERIMENTAL PRODUCTION OF CHANGES IN THE LARGE INTESTINES OF DOGS BY MEANS OF HEAT AND BY THE INJECTION INTO THEM OF VARIOUS IRRITATING SUBSTANCES.

By no means all of the experiments that have been made upon the large intestines of dogs with irritants are recorded in the following pages, for more than one test has been made in almost every instance, and in some cases four, six, eight, and even ten animals were sacrificed before a definite conclusion was arrived at as to the character of the lesions induced by the irritants in question. It was very early patent that should an attempt be made to describe the changes found in every animal experimented upon that this essay would be extended to an entirely unnecessary length, and it has therefore been the aim of the writer to select for record out of the several experiments made with each substance the one that appeared most typical.

CHAPTER I.

EXPERIMENTS TO DETERMINE THE EFFECTS OF A HIGH DEGREE OF HEAT ON THE LARGE INTESTINES OF DOGS.

EXPERIMENT I. **Intestine burned after death.**

A KNIFE was heated to a dull cherry-red color, and the sharp edge was lightly pressed for a moment against the mucosa of the large intestine of a dog after its removal from the animal's body. Where the knife came in contact with the tissue a scarcely perceptible grayish line was produced on its surface.

Microscopic specimens were prepared in the usual way, and on examination the following changes were noted: At the points where the burns were made there are distinct depressions upon the surface of the mucosa. Covering these depressed areas there are layers of finely granular material containing small particles of mucin; this substance, however, lies all along the free surface of the intestine, and is here evidently not the result of the action of heat. After being stained by the usual methods the mucosa is found to be divided into four more or less distinct layers in the areas beneath the points where the burns were made. The first of these (*a*) lies immediately beneath the granular material just described, and consists of the tissues that have suffered most from the effects of the heat. Beneath this (*b*) there is an area that is almost entirely empty. Still further down (*c*) the tissues exhibit marked changes and present certain staining peculiarities hereafter to be referred to. The bases of the glands have not suffered so greatly as the tissues higher up, and, as a consequence, present almost a normal appearance and form the lowest layer (*d*) of the mucosa. The finer changes occurring in these different layers will now be considered in the order in which they have been mentioned.

(*a*) The tissues near the free surface of the mucosa exhibit marked alterations. The outer portion of this layer, which is in immediate contact with the granular material just referred to, consists of tissues that have in a large measure lost their nuclei and that stain in an almost uniform manner with acid dyes. The connective tissue fibrils are here fused together, forming highly granular, acidophilic masses in which the original cellular structures cannot be recognized. At a very short distance from the surface the tissues contain cells the nuclei of which stain even more intensely than normal with basic dyes. These nuclei, which evidently belong to the cells lying in the connective tissue, are considerably elongated and their long axes usually lie parallel to the surface of the intestine. The connective tissue fibrils preserve here their usual appearance in a degree, but are swollen and usually greatly distorted. In the lower portion of this badly burned area there are always one or two of the crypts of Lieberkuehn, the ends of which have evidently been turned over by the pressure exerted by the knife while the burn was being made. The crypts contain hardly a vestige of the epithelial cells that originally lined them. At the edges of the burnt area the epithelial cells in the crypts have not undergone such extensive alterations, but it is noteworthy that the mucin is far better preserved than any of the other constituents of the cells. The nuclei of the cells lying between the crypts in the deepest portion of the badly burned region show a certain degree of elongation, but their long axes are usually transverse to the surface of the gut. The connective tissues are here likewise considerably swollen.

(*b*) The open spaces beneath the areas just described lie on a level that about corresponds to the necks of the crypts; in the fresh state they probably contained a certain amount of steam, and, if not this, certainly more or less liquids, as they are in a great measure empty. In no instance, however, do they entirely separate the deeper tissues from those that lie above, for at some points small strands of collagenous tissue pass through the cavities and unite them together. The tissues that line the spaces present an exceedingly ragged appearance on all sides, indicating in an unmistakable manner that they were violently torn asunder.

(*c*) The tissues that lie beneath these cavities are not so much altered as those nearer the surface, but nevertheless present a considerable degree of change. The crypts, where they abut on the open spaces, are always diminished in calibre owing to swelling of the structures that lie between them. In these situations the external coats of the epithelial cells lining the crypts have universally ruptured, and the cells have the appearance of being fused together; their nuclei are irregular in form, being elongated and often twisted, and take the basic stain feebly. It is a curious fact that the masses of mucin that normally occur in the cells in these situations preserve their form, and, in most instances, even their relative position to each other. The lumina of many of the crypts are completely filled with free mucin and disintegrated cells. Lower down the cells of the crypts still present no distinct outlines. The nuclei of these cells are very much elongated and their long axes are always parallel, or nearly so, to the long axes of the crypts; they take the basic stain with great intensity. The connective tissues that intervene between the crypts at some distance from the open spaces do not show a great degree of change, but both the collagenous and elastic tissue fibres take the stain poorly, and they are in many instances swollen. The lymph spaces between the fibres are distinctly increased in size and evidently contained either small quantities of water or, what seemed much more likely, minute collections of steam; the cells that lie in these situations are irregular in form and are oftentimes decidedly swollen. The cells found in the interstitial tissues at these points, however, as a rule, show no alteration, and it is to be especially noted that their nuclei do not show that elongation that invariably occurs in the neighboring epithelial cells.

(*d*) The epithelial cells lining the bodies of the crypts in the areas just beneath where the burns were made have generally desquamated, and in many instances the walls of the cells have ruptured; the lumina of the crypts contain quantities of granular débris that results from this process. In these instances, however, in which the cells contain mucin this substance presents an entirely normal appearance. The tissues intervening between the bases of the crypts show no alteration.

The other coats of the intestine are entirely unaltered.

Quite a number of specimens were prepared and examined that were burned with the sharp edge of a knife fifteen minutes before the death of the animal whose intestine was being operated upon.

On microscopic examination none of these showed alterations different in any way from those found in instances where the intestine was burned after death, and a separate description of the changes is therefore considered unnecessary.

Other specimens were prepared by burning the intestine in a similar manner six hours before death. On microscopic examination the alterations are found to agree in every particular with those already described, with the exception only that the bloodvessels in the vicinity are dilated and in many cases ruptured, and that the tissues at the edges of and immediately beneath the lesions are found to be somewhat swollen as the result of the presence of a certain amount of effused blood, from the collection in the parts of fluids, and the presence of quite a number of polymorphonuclear leucocytes; these changes are confined to the immediate vicinity of the alterations and do not extend to any great distance into the surrounding tissues.

EXPERIMENT II. **Heat. Duration, six hours.**

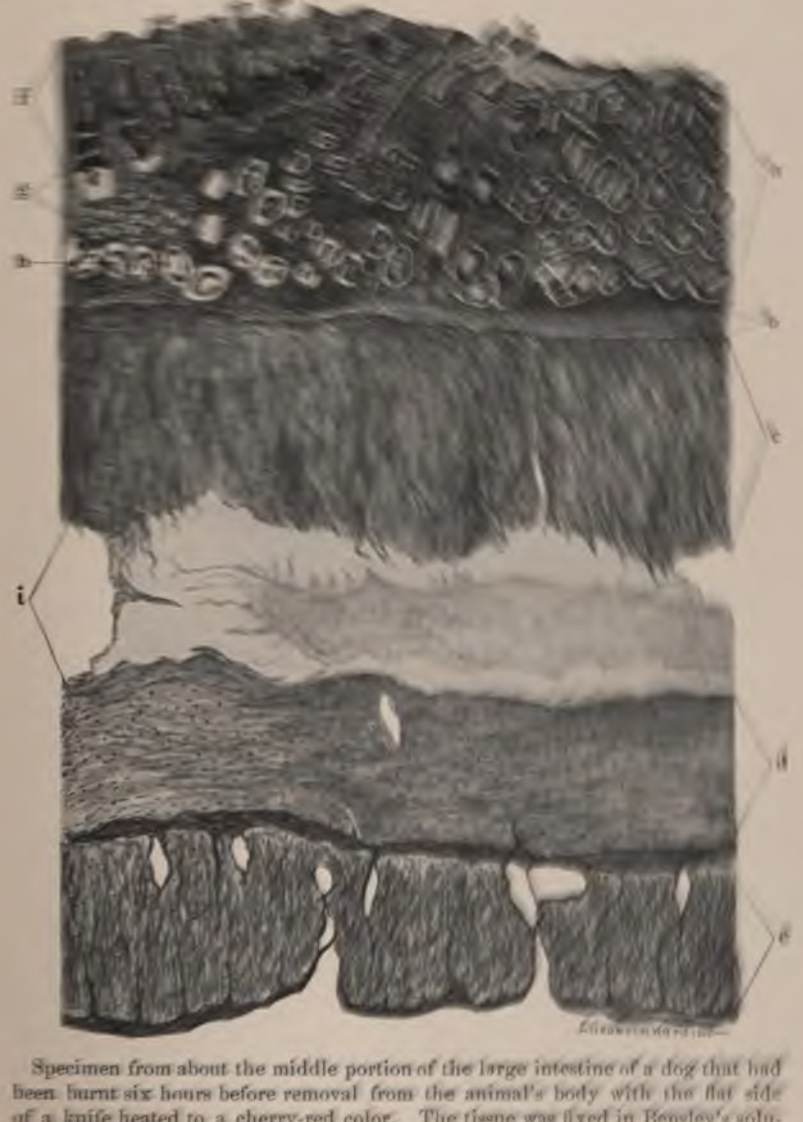
The blade of a knife was heated to a cherry-red color, and its flat surface was applied for a moment to the mucous surface of a dog's intestine. Six hours later the tissue was removed. The wall of the gut at the point where the burn was made was distinctly swollen; the surface of the intestine was of a grayish color, and surrounded by an area of marked redness.

On microscopic examination it is found that the tissues lying at a short distance from the edge of the burn show no alteration.

Somewhat nearer the only changes found are a dilatation of the bloodvessels of the interglandular substance, and as the margin of the burnt area is approached it is found that, in addition to the dilatation of the bloodvessels,quite a number of polymorphonuclear leucocytes have collected in the parts, and the epithelial cells covering the surface of the mucosa and those lining the underlying crypts exhibit catarrhal change; the capsules of these desquamated cells seem to have ruptured in many instances, and the protoplasm has been discharged, leaving the nucleus in an apparently normal condition. The deeper tissues of the intestinal wall show beneath these areas practically no change. In the edges of the burnt region the pre-existing tissues have completely disappeared; the epithelial cells that covered the surface, and those that lined the crypts, and the interglandular substance have all entirely disintegrated, and in their stead there is found a mass of polymorphonuclear leucocytes, lymphoid cells, pseudoplasma cells, and a few mucinoblasts. It is rather remarkable that in this zone not even a vestige of the crypts remains. Similar alterations are present in the muscularis mucosæ, the fibrils of which have been almost entirely replaced by cellular collections corresponding to those found more superficially. The tissues of the submucosa lying immediately beneath are considerably swollen, this being the result of the accumulation of fluids in the parts and of the presence of a considerable amount of hemorrhage; there are likewise found here a few polymorphonuclear leucocytes, quite a number of lymphoid cells, many plasma cells, and a few large phagocytes and mucinoblasts. The red blood-corpuscles that have been effused into the tissues have generally, in greater or less degree, degenerated, so that there is often found an acidophilic granular débris representing them. The tissues contain also a great amount of fibrin. The pre-existing collagenous tissues of the parts stain in an almost normal manner and the elastic tissue fibrils exhibit no alteration.

The layer of the submucosa above described in which the pre-existing tissues have been entirely replaced by cells is exceedingly thin, measuring, as a rule, not more than 100μ in thickness. Internal to it—*i. e.*, toward the central portion of the burn—the superficial structures, with the exception of the surface epithelium, still remain in their normal situations, and, though greatly altered, may be always recognized; the surface epithelial layer, and the basement membrane upon which the cells lie, have entirely disappeared. The tissues lying on and near the surface have been so altered that they have lost, in a large measure, the property of taking basic stains, and appear as an almost homogeneous, hyaline layer occupying the outer half of the mucosa. In the lower portion of this layer particles of mucin lying within

PLATE V.



Specimen from about the middle portion of the large intestine of a dog that had been burnt six hours before removal from the animal's body with the flat side of a knife heated to a cherry-red color. The tissue was fixed in Bensley's solution and stained by the method of Van Gieson. Beck ¼ inch, Oc. 1 inch. *a.* Mucosa. *b.* Muscularis mucosæ. *c.* Submucosa. *d.* Circular muscular layer. *e.* Longitudinal muscular layer. *f.* Edge of the burnt area in mucosa. *g.* Masses of cells separating the burnt tissues from those that are but little changed. *h.* Masses of desquamated epithelium in the deeper portions of the crypts below the burnt area. *i.* A collection of albuminous liquid containing fibrin separating the submucosa from the circular muscular layer. (Exp. II.)

the remnants of the epithelial cells still stain in a normal way. This hyaline coat gradually merges into a layer in which the cells have been evidently fixed by heat after a fashion; the tissues here preserve in a large measure their normal appearance and take basic stains in the usual way. On close inspection it is invariably found that the epithelial cells lining the crypts have apparently amalgamated together, and that their nuclei are often greatly distorted; in many instances these nuclei are rod-shaped and their long axes lie parallel to the long axes of the crypts in which they lie. The mucin in the mucin-bearing cells stains in a normal way. The glands are much compressed as a result of the alterations in the intervening substance at these points.

The bloodvessels of the interglandular substance lying between the partially preserved glands just described have universally ruptured, and there is often present great quantities of disintegrated blood in these tissues. In addition to the cells that are normally found in the parts there are also numerous polymorphonuclear leucocytes. The elastic tissues found in this region are excellently preserved, but the collagenous tissues have entirely disappeared.

The basal portions of the glands show alterations similar to those that were described as occurring throughout the glands immediately surrounding the burnt area. These changes consist in shedding off of the epithelial cells and the disappearance of their protoplasm, leaving in most instances the nuclei intact. The basement membranes upon which these cells lie are normal.

The interglandular substance surrounding the deeper portions of the crypts is composed of the cells that are normally found in the parts, with the addition of a considerable amount of hemorrhage and many polymorphonuclear leucocytes.

The fibres of the muscularis mucosæ have been in a large measure replaced by polymorphonuclear leucocytes, the tissues composing this layer apparently having undergone solution and disappeared.

The tissues of the submucosa that lie immediately beneath the muscularis mucosæ are greatly swollen; this is a result of the presence of fluids and of great numbers of polymorphonuclear leucocytes. The bloodvessels in these situations are dilated and filled with blood, and multitudes of polymorphonuclear leucocytes are always attached to the inner coats and in many instances may be seen lying within their walls. There is a small amount of hemorrhage in these tissues. Both the collagenous and elastic tissue fibrils stain well. The tissues constituting the deeper portions of the submucosa are likewise greatly swollen, this being the result in a large measure of extensive hemorrhages into the parts. The red blood-corpuscles are usually in a partially degenerate condition wherever they are found lying loosely in the tissues of the submucosa. In the deeper portions of the submucosa there are extensive deposits of fibrin.

The circular muscular layer and the submucosa have been torn asunder by the accumulation between them of great quantities of an albuminous liquid; this liquid contains fibrin, but practically no cells.

The remaining coats of the intestine show no alteration.

Résumé of the Changes Produced in the Dead Tissues by Heat.

As a result of the changes described the burnt tissues present quite a characteristic general appearance under low powers of the microscope; externally they contain practically no nuclei, and all of the structures present stain with acid dyes. Somewhat lower down numerous cells are present, the nuclei of which stain with great intensity with basic dyes, and the intervening tissues are normally acidophilic. Beneath this there is an open space through which run shreds of more or less altered connective tissue. Still lower down there is an area in which the nuclei of the epithelial cells are much elongated, have their long axes parallel to the long axes of the glands, and stain very poorly, and the lumina of the crypts are filled with the granular débris that results from the disintegration of the epithelial cells. The intervening connective tissue is swollen, oftentimes to such an extent that the upper portions of the lumina of the crypts are almost entirely obliterated. Somewhat beneath this, and forming the lower border of this layer, the nuclei are stained with considerable intensity, but in every other way the cells of the crypts resemble those of the portions of the glands higher up. The cells that lie in the bases of the crypts have in many instances degenerated and have very generally shed off from their basement membranes.

Changes Produced in the Living Tissues by Heat.

Where the knife came in actual contact with the tissues they were completely destroyed and have entirely disappeared. The structures beneath were acted upon in such a way that they have become practically acidophilic throughout; they have in a large measure lost their morphologic peculiarities, and appear as a more or less homogeneous, hyaline mass covering over the partially preserved tissues that lie underneath. As might be expected, the collagenous tissue fibrils can no longer be recognized, but the threads of elastic tissue stain in a more or less normal way. The only portions of the epithelial cells that are preserved in the parts are the particles of mucin contained within some of them. Lower down these almost completely destroyed tissues merge into structures that are fairly well preserved, the heat having acted to a certain extent upon them as a fixative. In this area the epithelial cells lining the crypts appear to have coalesced, and their nuclei are greatly distorted. Sometimes these nuclei are rod-shaped, and they not uncommonly lie with their long axes parallel to the long axes of the crypts. The basement membranes of these portions of the glands are normal.

The tissues that normally intervened between these glands have been in a large measure replaced by blood, which has been effused into the parts in great quantities; the pre-existing cells of the part are present in about the usual number.

Lower down in the glands the epithelial cells have shed off, the cellular membranes appear to have ruptured in most instances, and the protoplasm, as a consequence, has been liberated.

In the intervening tissues there are large numbers of polymorphonuclear leucocytes.

Beneath the burnt areas the fibres composing the muscularis mucosæ have in a large measure disappeared, but the elastic tissue fibrils appear to have suffered no change. Replacing the muscle fibres there are a great many polymorphonuclear leucocytes.

The portions of the submucosa that lie in the vicinity of the muscularis mucosæ are swollen, contain great numbers of polymorphonuclear leucocytes, and quite an amount of free blood. The deeper layers of this coat contain enormous quantities of disintegrating blood and much fibrin. Albuminous fluids have collected in considerable quantity between the submucosa and the circular muscular layer.

None of the other coats of the intestine presents abnormalities.

Immediately around the edges of the burnt area the pre-existing tissues of the mucosa have entirely disappeared, being replaced by polymorphonuclear leucocytes in a large degree. Somewhat further outward the bloodvessels are dilated, and there is quite an amount of hemorrhage into the tissues.

CHAPTER II.

EXPERIMENTS TO DETERMINE THE EFFECTS PRODUCED ON THE LARGE INTESTINES OF DOGS BY THE INJECTION OF ALKALINE SOLUTIONS.

EXPERIMENT I. **Dilute liquor potassæ. Duration, twelve hours.**

ON January 31, 1900, there were injected into the rectum of a dog 10 c.c. of liquor potassæ (U. S. P.), diluted with an equal quantity of water. Twelve hours later the animal was killed with chloroform, and an autopsy was at once made.

On examination the lower part of the intestine was found to be almost empty, and the mucosa was uniformly reddened. In this situation there were many transverse rugæ on the surface of the gut, the apices of which showed no more redness than the surrounding surface of the intestine.

On microscopic examination it is found that the superficial epithelium that normally covered the mucosa has entirely disappeared in the affected region, and the outer half of this coat is in a semi-necrotic condition. The epithelial cells lying in this situation have entirely disintegrated, and there remains in their stead a mass of granular débris, intermingled with which there is much mucin in all instances; however, the mucin here found does not stain altogether so brilliantly as that present in the lower part of the crypts, and it is evident that it is more or less altered. The average diameter of the crypts in this situation is decidedly decreased, this being due to the accumulation of cells and fluids in the interglandular substance. In this part of the mucosa the elastic basement membranes have in all instances entirely disappeared. The tissues that lie between the crypts are in a large measure acidophilic, the only exception to this being the nuclei of the polymorphonuclear leucocytes that evidently migrated into the parts after the maximum deleterious action of the liquor potassæ had passed away. The bands of pre-existing collagenous tissue can always be made out in the diseased situations; they are distinctly swollen and do not present the sharp outlines that they exhibit in health. The pre-existing lymphoid cells, the pseudoplasma cells, and the mucinoblasts that are normally found in these situations have become entirely necrotic, and, as before remarked, the only cellular constituents that appear normal are the multitudes of polymorphonuclear leucocytes that have penetrated into the parts. The walls of the bloodvessels have likewise undergone a complete necrotic change, and much of the blood that was contained in them has been widely diffused into the interstices of the interglandular substance; in many situations masses of partially degenerated red blood-cells may be found lying loosely in the tissues, but these cells have, as a rule, become so completely necrotic that they can no longer be recognized with certainty.

The epithelial cells that line the crypts in the area immediately beneath the necrotic layer just described present the usual changes that occur when they are subjected to irritation, being swollen, irregular in form, and in many instances completely detached from their basement membranes, and lie loosely in the lumina of the crypts. Some of them have evidently entirely disintegrated; for there is always present a considerable quantity of granular débris surrounding them. Within the lumina of the crypts there is invariably found much mucin. In some instances mucin formation has gone on to such a degree that this substance completely fills the lumina of the crypts, and has exerted such a pressure upon the surrounding cells that they appear greatly diminished in size and lie compressed against their more or less necrotic basement membranes; under these circumstances those nuclei of the cells that are oblong lie parallel to the long axes of the crypt, and not transversely as in health. In instances where the mucin formation has been extreme almost the entire crypt is taken up by the plugs of mucin that lie within them, these measuring in diameter oftentimes as much as 60μ—but a few microns less than the entire gland. None of the epithelial cells that are found in this area ever show in their protoplasm any evidence of mucin being present. The cells lining the basal portions of the crypts generally appear somewhat swollen, and in some instances they have shed off from their basement membranes; but further than this no alteration in these parts of the glands is apparent. The basement membranes that line the bases of the crypts still stain in a fairly normal way, but the tissues of which they are composed lose their power of taking the usual dyes a short distance from the deepest portion of the glands. In the interstitial tissues lying immediately beneath the necrotic area the bloodvessels are enormously enlarged and are filled with blood, but further than this the tissues practically present no alteration. The line of demarcation between the diseased tissues and those that lie beneath them is always exceedingly abrupt. The tissues lying beneath the basal portions of the glands show no alterations.

The muscularis mucosæ is normal.

The bloodvessels lying in the portion of the submucosa in the vicinity of the muscularis mucosæ are generally somewhat dilated and are filled with blood. No other change is found in the submucosa.

The other coats are entirely normal.

EXPERIMENT II. **Liquor potassæ. Duration, twenty-four hours.**

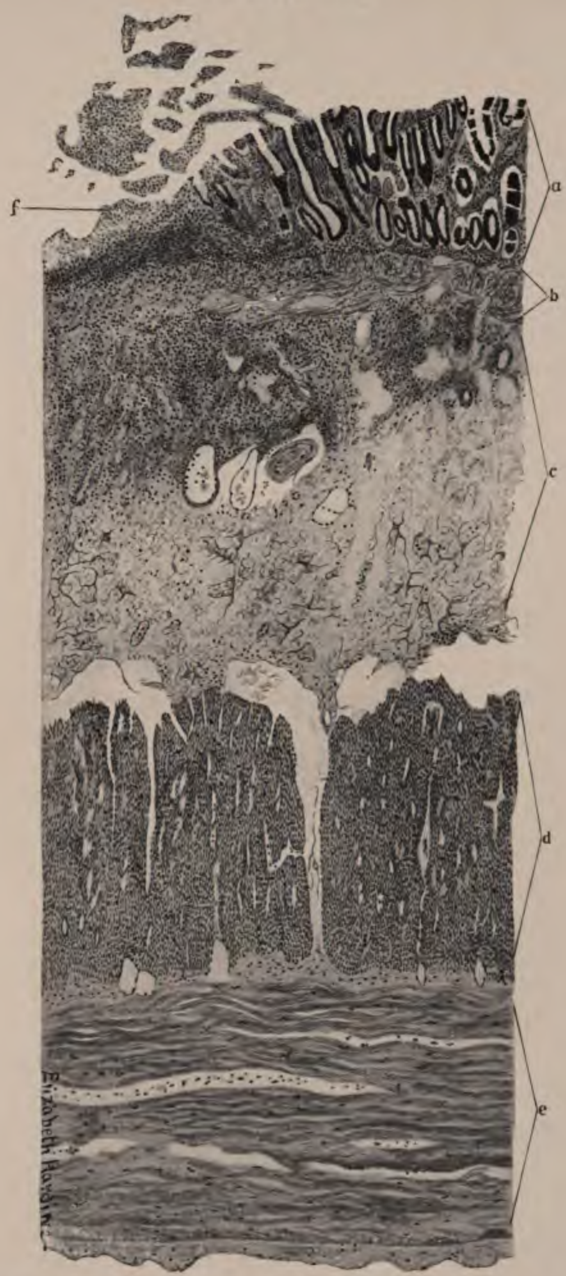
At 1 P. M., on November 27, 1900, 10 c.c. of liquor potassæ were injected into the rectum of a dog weighing about 6 kg. Twenty-four hours later the animal was killed with chloroform, and an autopsy was at once made. The large intestine was empty, but only the lower half showed obvious alteration. In this region the mucosa was covered with a thick layer of mucus, and its surface presented a grayish appearance, mottled with small, pinkish-colored spots. The rugæ were largely obliterated, and even where present the changes were no more marked on their tops than in other parts of the neighboring mucosa.

On microscopic examination the surface layer of epithelium covering the mucosa is found to be generally absent, though small areas are here and there found in which the epithelial cells have not desquamated and appear entirely normal. Where the surface epithelium shows no change the tissues that lie beneath are practically unaltered, with some exceptions hereafter to be referred to, and for this reason description is only necessary for those regions in which superficial necrosis of the epithelium has occurred. The changes in the mucosa vary much in different situations, there being in some places necrosis only of the surface epithelium and of the lining cells of the mouths of the crypts, while in others the entire mucosa is destroyed. In some areas the mucosa is represented by a mass of cells intermixed with which is much granular débris, the elements normal to the parts having completely sloughed away. Lying along the free surface of the intestine there are always found collections of epithelial cells and polymorphonuclear leucocytes; these cells do not show any marked degree of alteration, as they preserve in a large measure their normal morphologic peculiarities and stain in the usual way. In those parts of the mucosa where only the upper portions of the crypts have been entirely destroyed the epithelial cells remain attached to their basement membranes and preserve their normal form; it is noteworthy, however, that no mucin is present in these cells, and that their protoplasm stains somewhat more deeply with basic dyes than is normally the case. Mitotic figures are comparatively rare in these cells. In regions where the crypts have been almost entirely destroyed the epithelial cells that appear in the remnants of these structures have shed off from their basement membranes, and are round or irregular in form; they however still preserve their normal staining reactions.

The elastic tissue basement membranes of the diseased crypts no longer take their specific stains, though they can in some instances still be made out as very delicate, finely hyaline structures lying in the situations that they normally occupy.

The changes in the interstitial tissues vary considerably, and depend upon the extent of the alterative process. In those areas where only the superficial epithelium has been eroded away the tissues that lie beneath show practically no alteration with the exception that the bloodvessels are considerably dilated and that there are a few polymorphonuclear leucocytes in the lymph spaces. Where the changes have been more extensive the bloodvessels are in all instances enormously dilated and have not infrequently

PLATE VI.



Specimen from about the middle portion of the large intestine of a dog into which a dilute solution of liquor potassæ had been injected twenty-four hours before the tissues were removed from the animal's body. The tissues were fixed in Bensley's solution and stained with carbol toluidin-blue and eosin. Beck ¼ inch, Oc. 1 inch. *a.* Mucosa, the structures of which have been entirely replaced by polymorphonuclear leucocytes, red blood cells, lymphoid cells, large phagocytes and mucinoblasts at (*f*). *b.* Muscularis mucosæ, which is swollen and contains numerous polymorphonuclear leucocytes. *c.* Submucosa, which is much swollen and contains many polymorphonuclear leucocytes and much fibrin; this layer is partially separated from the circular muscular layer by collections of liquid. *d.* Circular muscular layer. *e.* Longitudinal muscular layer. (Exp. II.)

ruptured. There are found in the tissues, as a consequence, numerous red cells, and there are always present considerable numbers of polymorphonuclear leucocytes; lymphoid cells, large phagocytes (epithelioid cells), and a few plasma cells are likewise encountered. Mucinoblasts are especially large and frequent in all parts of the diseased mucosa. As has been before remarked, these changes frequently extend through the mucous coat, and under these circumstances the surfaces of the resulting ulcers consist of more or less necrotic connective tissue, intermingled with which there are large numbers of cells, principally polymorphonuclear leucocytes.

The muscularis mucosæ is considerably swollen, this being particularly the case in those areas where the necrotic process has extended deeply into the mucosa. The lymph spaces between the muscle fibres are more or less dilated, contain quite a number of polymorphonuclear leucocytes, and in the fresh state were evidently distended with fluids. The muscle fibres of this layer present no obvious alterations, but almost everywhere the elastic tissue fails to take its specific stains.

The submucosa shows a very marked degree of swelling. The lymph spaces are enormously dilated, contain a few polymorphonuclear leucocytes, and large quantities of fibrin. The collagenous tissue in this layer stains in a normal manner, but the fibrils of elastic tissue do not take their specific stains. These changes are universally present in all parts of the submucosa examined—even beneath those areas where the tissues lying above are entirely normal.

The muscular, subserous, and serous coats show no change.

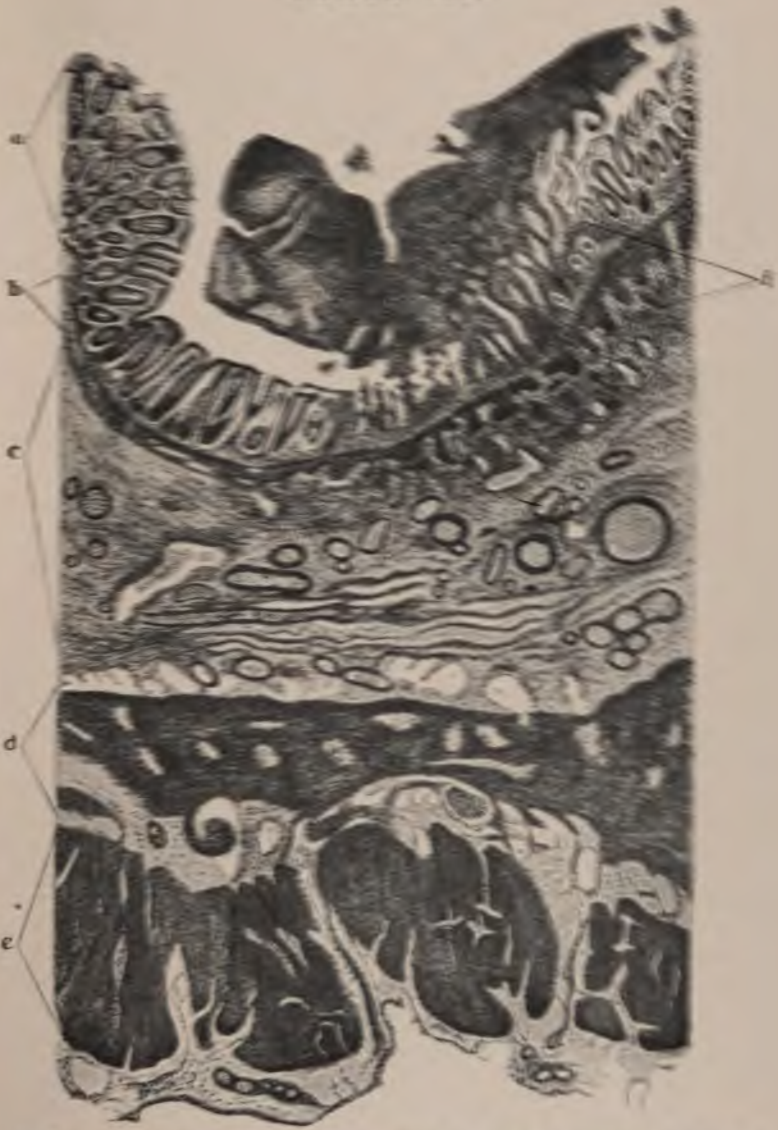
EXPERIMENT III. **Liquor potassæ. Duration, twenty days.**

On December 11, 1900, a dog weighing about 5 kg. was given 10 c.c. of liquor potassæ (U. S. P.) by the rectum. On the following day the animal appeared perfectly well, and had apparently suffered no ill effect as a result of the administration of the drug. On December 14th the injection was repeated. On the following day the dog passed a considerable quantity of bloody mucus and presented unmistakable evidence of being ill. On December 17th

10 c.c. of liquor potassæ were again administered. No more injections were given until December 23d, for the reason that the dog that was receiving the acid injections was so weak that it appeared unwise to repeat the dose earlier, and it was thought best for the sake of uniformity to make the administrations of the acid and alkali correspond as closely as possible. Another injection was given on December 28th. On December 31st the animal was killed with chloroform, and an autopsy was at once made. The lower half of the large intestine was found empty, but the upper portion contained a small amount of fecal matter. The walls of the lower half of the gut appeared somewhat thickened. The transverse rugæ in this situation were quite prominent, but the mucous membrane covering their apices did not appear so red as that found on the intervening portions of the surface of the intestine; although the entire mucosa appeared decidedly discolored, there was at no point appearance of ulceration.

On microscopic examination it is found that the surface of the gut is beset with numerous ulcers—the mucosa in these areas being always practically destroyed—while the intervening portions show, as a rule, but little change; indeed, it may be said that the entire wall of the gut is normal in those areas where ulceration does not exist—if a mild degree of dilatation of the vessels that lie between the crypts be excepted. At the margins of the ulcers this practically normal mucosa ceases abruptly, and it is noteworthy that the epithelial cells lining the crypts, as well as the intervening surfaces, show even at the very edges of the lesions no alterations of moment. In the ulcerated regions the mucosa has in almost every instance entirely disappeared, though here and there the basal portions of the glands are, although much altered, still preserved. The epithelial cells that lined these remnants of Lieberkuehn's crypts have, under these circumstances, largely desquamated, and in all stages of disintegration lie grouped together in the lumina of the glands. Mixed with these necrotic cells a small amount of free mucin is sometimes found. Occasionally a new formation of epithelial cells has occurred in these vestiges of the crypts; under such circumstances the newly-formed cells are flattened, are exceedingly irregular in form, and within them no mucin is found.

PLATE VII.



Specimen from about the middle portion of the large intestine of a dog into which a dilute solution of liquor potassæ had been injected twenty days before the tissues were removed from the animal's body. The tissues were fixed in Bensley's solution, and stained with carbol toluidin-blue and eosin. Beck ⅙ inch, Oc. 1 inch. *a.* Mucosa, the structures of which have been replaced by polymorphonuclear leucocytes at (*f*). *b.* Muscularis mucosæ, which is swollen and contains quite a number of polymorphonuclear leucocytes in some situations. *c.* Submucosa, which is swollen, contains numerous polymorphonuclear leucocytes, mucinoblasts, lymphoid cells, and many plasma cells *d.* Circular muscular layer. *e.* Longitudinal muscular layer. (Exp. III.)

The tissues that originally lay between the crypts have practically disappeared, but there remains in their stead an enormous number of polymorphonuclear leucocytes, mixed with which there are a few lymphoid cells. These cellular masses forming the coverings of the ulcers are always considerably thicker than the surrounding mucosa, and in almost every instance project beyond and overhang the neighboring surface of the gut. The muscularis mucosæ in the affected regions is pushed downward by the swelling of the submucosa. Between the muscle fibres that go to make up this layer there are considerable collections of fluids and great numbers of polymorphonuclear leucocytes; the muscle fibres themselves show no apparent alteration. In some situations the elastic tissue network of this layer does not take the stain in the usual way, and in the regions most diseased has apparently entirely disappeared.

The layer of the submucosa next to the muscularis mucosæ is considerably swollen. This swelling is due to a mild degree of dilatation of the lymph channels and spaces, and, in addition, there is a considerable increase in the collagenous tissues found in the parts. In the lymph spaces there are many polymorphonuclear leucocytes and lymphoid cells, a few mucinoblasts, and a considerable number of plasma cells. Deeper portions of the mucosa are likewise to a certain degree swollen, but polymorphonuclear leucocytes are only found in this situation immediately around the bloodvessels; there are also present a few lymphoid cells and quite a number of most exquisite plasma cells. The collagenous tissues are here likewise somewhat increased.

No changes are found in either of the muscular coats, the subserous or serous coat.

EXPERIMENT IV. **Solution of sodium hydroxide. Duration, twenty-four hours.**

On January 7, 1901, there were injected into the rectum of a dog 10 c.c. of a solution of sodium hydroxide that corresponded in strength with the liquor potassæ of the U. S. P. Exactly

The tissues that originally lay between the crypts have practically disappeared, but there remains in their stead an enormous number of polymorphonuclear leucocytes, mixed with which there are a few lymphoid cells. These cellular masses forming the coverings of the ulcers are always considerably thicker than the surrounding mucosa, and in almost every instance project beyond and overhang the neighboring surface of the gut. The muscularis mucosæ in the affected regions is pushed downward by the swelling of the submucosa. Between the muscle fibres that go to make up this layer there are considerable collections of fluids and great numbers of polymorphonuclear leucocytes; the muscle fibres themselves show no apparent alteration. In some situations the elastic tissue network of this layer does not take the stain in the usual way, and in the regions most diseased has apparently entirely disappeared.

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No changes are found in either of the muscular coats, the subserous or serous coat.

EXPERIMENT IV. **Solution of sodium hydroxide. Duration, twenty-four hours.**

On January 7, 1901, there were injected into the rectum of a dog 10 c.c. of a solution of sodium hydroxide that corresponded in strength with the liquor potassæ of the U. S. P. Exactly twenty-four hours after the injection was given the animal was killed with chloroform, and an autopsy was at once made.

The large intestine contained fecal matter in its upper portion, but the lower half of the bowel was empty. On examination it was found that the mucosa of the lower part of the intestine was somewhat reddened and that the area presenting this change corresponded closely with the portion of the gut that was empty. The rugæ were not so prominent as is usual, and the mucosa covering them did not appear more greatly affected than that overlying the neighboring portions of the gut. The walls of the bowel in this region were decidedly swollen.

On microscopic examination the mucosa of the intestine in the diseased area is found to be in a state of advanced necrosis. This layer, however, is not affected completely through in a uniform manner, for it may be distinctly divided into two separate and distinct portions—an upper, in which immediate death evidently followed the application of the alkali, and a deeper, in which the tissues did not suffer so severely, but have nevertheless undergone great alteration. The entire mucosa is greatly swollen, this applying especially to the deeper portion just referred to. Sections were made through the point at which the necrotic tissues came in contact with those that were normal, and the transition is found to be very abrupt; the normal tissues lie in direct contact with those that have undergone complete necrosis. In the diseased regions the superficial epithelium covering the mucosa has entirely disintegrated and sloughed away. The epithelial cells that line the mouths and necks of the crypts have likewise undergone complete degenerative change, but the granular débris resulting still remains in the lumina of the crypts to which the cells belonged. This granular débris is acidophilic throughout, and at no point are any distinct cellular elements to be made out within it; mixed with it there are here and there small particles of mucin, but this substance is almost entirely absent, and even that which is present does not stain in a perfectly normal way. The tissues lying between the remnants of the crypts are likewise in a state of advanced degenerative change, are uniformly acidophilic, and none of the structures present show any of the peculiarities that are characteristic of those that are normally found in the parts.

Between the superficial layer of the mucosa and the deeper one, in which the changes are not so greatly advanced, there is a thin stratum of tissue in which the nuclei of the cells of the interstitial substance stain deeply, and, in addition, the other tissues of the parts are decidedly basophilic, there being thus produced in sections properly prepared a dark line separating the two layers from each other.

Notwithstanding that the alterations in the deeper portions of the mucosa are not so marked as in the more superficial parts, the changes are still of a pronounced character. The crypts are widely separated from each other by masses of inflammatory exudate, and the cells lining them exhibit unmistakable evidences of degeneration. The outlines of the epithelial cells lining the lower portions of the bases of the crypts cannot, as a rule, be made out, and the cells are represented by masses of granular material in which nuclei may be occasionally found; the cells have so greatly swollen that the lumina of the crypts are in most instances entirely obliterated. Mucin formation is never observed in the cells of these crypts, but very rarely a small amount of this substance is found lying free in the lumina of the glands.

The elastic tissue basement membranes around these crypts do not, as a rule, stain well, but in properly prepared sections may be always discerned.

Between the crypts there are a great many polymorphonuclear leucocytes and considerable numbers of lymphoid cells, intermingled with which there are here and there a few red blood-corpuscles; in the fresh state the tissues evidently also contained large quantities of fluids. Mucinoblasts are never found in these situations. The fibrils of collagenous tissue stain in the usual way and do not appear to be altered to any extent. The smaller bloodvessels lying in these areas are considerably dilated and contain more than the usual number of polymorphonuclear leucocytes; in some instances they have ruptured.

The muscle fibres that go to make up the muscularis mucosæ are widely separated from each other by collections of fluids and by great numbers of polymorphonuclear leucocytes. The individual muscle fibres, however, show no obvious alteration.

In the layer of the submucosa just beneath the muscularis mucosæ there are numbers of polymorphonuclear leucocytes, many lymphoid cells, and a few mucinoblasts, and, in addition, there are in the regions most affected great quantities of fibrin. The polymorphonuclear leucocytes and fibrin are not uncommonly found in the larger lymph channels. The bloodvessels in this region are usually dilated and are filled with blood. These changes in some instances extend completely through the submucosa, but in most situations the deeper portions of this layer, while showing changes similar to those just described, are by no means so greatly affected.

In many areas the circular muscular layer contains considerable quantities of fluids that push the fibres more or less apart, and small collections of polymorphonuclear leucocytes here and there; further than these there are no obvious alterations.

The longitudinal muscular layer shows to a less degree changes that are similar to those just described as occurring in the circular muscular layer; however, in most situations this coat is entirely normal.

The subserous and serous coats present no alteration.

EXPERIMENT V. **Solution of ammonium hydroxide. Duration, twenty-four hours.**

On January 15, 1901, 10 c.c. of a solution of ammonium hydroxide that corresponded in strength with the liquor potassæ of the U. S. P. were injected into the rectum of a medium-sized dog. Twenty-four hours later the animal was killed with chloroform, and an autopsy was at once made. The large intestine was filled with feces; the lower part of the gut was swollen, the rugæ numerous, and the mucosa was distinctly reddened, but there was no evidence of necrotic change.

On microscopic examination the superficial epithelium covering the mucosa is found to be entirely absent in the regions most affected, and not uncommonly the cells that lay in the mouths and necks of the crypts have entirely sloughed away. The superficial layer of the interglandular substance has likewise become necrotic and has disappeared. Generally the greater portions of the bodies and always the bases of the crypts are partially preserved, but even here the cells lining them show marked alterations. Between the deeper portions of the glands the supporting structures do not exhibit correspondingly extensive changes. Toward the free ends of these partially preserved crypts the epithelial cells show evidences of most pronounced degeneration, and have generally become completely necrotic; the granular débris that results from this disintegration of the epithelial cells is still found in the lumina of the crypts. Deeper down the cells are here and there fairly well preserved, but even in the basal portion of the glands they are swollen, irregular in form, and their outlines are very indistinct; the cells here, however, have nuclei that stain in the usual way. As is always the case in tissues that have been subjected to the action of alkalies, mucin formation is going on to a very limited degree in the epithelial cells of the affected glands, this substance, as a rule, being absent from their lumina. The elastic tissue basement membranes of the crypts do not take their specific stains in the usual way, and in many instances appear to have disappeared.

The tissues lying between the diseased crypts are considerably swollen, this being evidently due to dilatation of the small bloodvessels—which condition is very pronounced—collections in the parts of fluids, and to the infiltration of great numbers of polymorphonuclear leucocytes; in addition to the polymorphonuclear leucocytes, quite a number of lymphoid cells and a few plasma cells are found. Mucinoblasts nowhere occur in the interglandular substance. With the exception that the elastic tissue fibrils do not take the stain, no other alterations are perceptible in these structures. Around the bases of the glands changes of a similar kind are observed, but the swelling is not so great and the polymorphonuclear leucocytes are not so numerous; the bloodvessels, however, in this region are greatly dilated and are filled with blood.

The muscularis mucosæ is slightly swollen. Between the muscle fibres composing the layer fluids have here and there collected, and there are present quite a number of polymorphonuclear leucocytes and a few lymphoid cells.

In some areas the superficial portions of the submucosa are somewhat swollen and contain quite a number of polymorphonuclear leucocytes, but the change is not very frequently observed. The bloodvessels, however, in this situation are usually dilated and filled with blood. In some of the larger lymph channels small quantities of fibrin are occasionally encountered, but this substance is by no means present to such an extent as is observed in inflammations induced by stronger alkaline substances.

The muscular, subserous, and serous coats are entirely unaltered.

Résumé of the Changes Produced as a Result of the Injection of Alkaline Solutions.

Very acute changes resulting from dilute liquor potassæ. (Twelve hours.) On post-mortem examination the large intestine was found to be almost empty, and the mucous surface on its lower half was distinctly reddened.

On microscopic examination it was found that the superficial layer of epithelium has entirely disappeared. The outer half of the mucosa is in a semi-necrotic condition. All of the pre-existing structures in this area show advanced degenerative change. There have migrated into the parts, especially where they come in contact with the practically normal tissues that lie beneath, great numbers of polymorphonuclear leucocytes. There has also been a considerable amount of hemorrhage into the tissues. The structures in the deeper half of the mucosa, while presenting alteration, still preserve in a great measure the peculiarities that characterize them in health. Within the lumina of the crypts there are great quantities of mucin, but none of the epithelial cells contain the slightest trace of this substance.

The bloodvessels lying in the interstitial substance between the bodies of the glands are enormously dilated and filled with blood. Further than this no changes of any importance are found.

Acute changes resulting from dilute liquor potassæ. (Twenty-four hours.) When the large intestine was removed its surface was found to be covered with mucus. The mucosa of the lower half of the gut was of a grayish color, with small pinkish spots scattered over its surface.

On microscopic examination it was found that the changes present vary considerably in different parts of the specimens examined. In some instances the destruction of the superficial epithelium and of the cells lining the mouths of the crypts has only occurred, while in other cases the entire mucosa has become completely necrotic. It is noteworthy that mucin is entirely absent from the epithelial cells lining the crypts in the affected areas.

Around the edges of the necrotic mucosa the tissues contain much effused blood, the result of the rupture of many bloodvessels in the diseased parts. The bloodvessels are all enormously dilated and filled with blood. The tissues contain polymorphonuclear leucocytes, plasma cells, lymphoid cells, large phagocytes, and numerous mucinoblasts.

The muscularis mucosæ is swollen and contains numerous polymorphonuclear leucocytes.

The tissues of the submucosa show a considerable degree of swelling, contain polymorphonuclear leucocytes, and, in many situations, fibrin. There were no changes of moment observed in the other coats of the intestine.

Acute changes resulting from a dilute solution of sodium hydroxide. (Twenty-four hours.) On examination the mucosa of the lower half of the large intestine is found to be decidedly reddened.

On microscopic examination the upper half of the mucosa was found to be in a state of advanced degeneration, and the remaining portion of this coat likewise showed marked alterations. In all instances the epithelial cells have shed off from the surface of the gut and from the mouths and necks of the crypts; the tissues intervening are entirely necrotic. In the bodies and bases of the crypts the epithelial cells are swollen, very irregular in form, and not uncommonly have shed off from their basement membranes; these cells never contain mucin within their protoplasm. This substance is not uncommonly found lying free in the lumina of the crypts. The lower portions of the glands are much compressed as a result of hemorrhage and of the accumulation of polymorphonuclear leucocytes and fluids in the surrounding tissues.

The interglandular substance of the deeper half of the mucosa is greatly swollen as a result of the presence of fluids. There are found within the tissues many lymphoid cells, numerous polymorphonuclear leucocytes, and a few red blood-cells lying loose in the tissues. Mucinoblasts are entirely absent.

The muscularis mucosæ is swollen, and there are between the fibres numerous polymorphonuclear leucocytes.

The outer portion of the submucosa contains numerous lymphoid cells, many polymorphonuclear leucocytes, a few mucinoblasts, and considerable quantities of fibrin. These changes become less marked deeper down in the substance of this coat.

The muscular coats are swollen and contain here and there polymorphonuclear leucocytes.

Acute changes resulting from ammonium hydroxide. (Twenty-four hours.) At the post-mortem the wall of the gut was found to be considerably swollen and its mucosa reddened.

On microscopic examination the superficial epithelium is found to have everywhere desquamated, and changes of a similar kind are usually observed in the mouths and necks of the crypts. In the deeper portions of the glands the epithelial cells are swollen, irregular in form, and have frequently shed off from their basement membranes; none of these cells contain mucin, and there is but little of this substance found in the lumina of the crypts.

The interglandular tissues are distinctly swollen, this being the result of the dilatation of many of the smaller bloodvessels and from infiltration into the parts of great numbers of polymorphonuclear leucocytes. Mucinoblasts are always absent.

The bloodvessels of the muscularis mucosæ and of the neighboring layer of the submucosa are distinctly dilated and are filled with blood. Many polymorphonuclear leucocytes are found in the interspaces of these tissues.

Chronic changes resulting from liquor potassæ. (Twenty days.) At the necropsy the wall of the gut was found considerably swollen and its mucous surface decidedly reddened. There were no macroscopic evidences of ulceration.

On microscopic examination there were found numerous small ulcers scattered over the surface of the intestine, and these lesions are, as a rule, sharply marked off from the surrounding practically normal structures. In the diseased areas the tissues that constituted the mucosa are found entirely necrotic in almost all cases, and, taking their places, is a granular débris, intermingled with which there are multitudes of polymorphonuclear leucocytes. In those instances where any parts of the glands remain in the affected areas the epithelial cells lining them show evidences of catarrhal change.

In the vicinity of the ulcers just described the muscle fibres of the muscularis mucosæ are pushed apart by great numbers of polymorphonuclear leucocytes and by the accumulation of fluids.

The tissues of the submucosa that lie immediately beneath the lesions just referred to are swollen and contain great numbers of polymorphonuclear leucocytes, many lymphoid cells, mucinoblasts, and plasma cells. Considerable new formation of collagenous tissue has occurred in these parts.

CHAPTER III.

EXPERIMENTS TO DETERMINE THE EFFECTS PRODUCED ON THE LARGE INTESTINES OF DOGS AS A RESULT OF THE INJECTION OF ACIDS.

EXPERIMENT I. **Dilute sulphuric acid. Duration, twelve hours.**

ON February 26, 1901, 10 c.c. of a solution of sulphuric acid were injected into the rectum of a dog; this solution consisted of 1 part of the acid to 189 parts of water. Twelve hours later the animal was killed with chloroform, and an autopsy was at once made.

The entire large intestine was found to be practically empty. The mucosa of the lower half of the bowel was reddened; the discoloration was uniform in the affected region. In the same part of the bowel there were numerous transverse rugæ. The walls of the lower half of the gut were decidedly swollen.

On microscopic examination it is found that the surface layer of epithelial cells has entirely shed off from the mucosa of the intestine, and not uncommonly changes of a like kind have occurred in the mouths and necks of the crypts. These shed-off cells may be sometimes seen lying along the surface of the mucosa; they are swollen and irregular in form, and their protoplasm is, as a rule, decidedly basophilic throughout, this being apparently the result of the breaking up of the nuclei, and the diffusion of their chromatin throughout the protoplasm of the cells. The cells that line the bodies and basal portions of the crypts have occasionally desquamated and present changes in every way similar to those that have been described as occurring in the surface cells; but more commonly they still remain attached to their basement membranes, and exhibit no alteration further than that their protoplasm is unusually basophilic. Lying between these cells polymorphonuclear leucocytes are not uncommonly encountered, and in some instances they have collected in considerable numbers in the lumina of the glands. The crypts are considerably compressed as the result of the accumulation of cells and fluids in the surrounding tissue. The basement membranes of the diseased crypts show practically no alteration.

Between the mouths and necks of the crypts the bloodvessels have universally ruptured and there lie between the glands great masses of blood. Polymorphonuclear leucocytes have also migrated into the parts in considerable numbers, and in some situations are quite as numerous as the red blood-corpuscles. The pre-existing cells of these tissues are still present, the mucinoblasts appearing to have even increased in number. The collagenous tissue fibrils are here so obscured by the effused blood that they can no longer be distinguished with certainty. As the deeper portions of the glands are approached these changes in the interglandular substance gradually decreases in severity until around the basal portions of the crypts there are no changes other than that there are quite a number of polymorphonuclear leucocytes intermingled with the preexisting cells of the part.

The muscularis mucosæ shows no alteration except that there are numerous polymorphonuclear leucocytes lying between the fibres composing the coat.

The layer of the submucosa that lies in the vicinity of the muscularis mucosæ contains numerous polymorphonuclear leucocytes and an unusual number of mucinoblasts. In this region the smaller bloodvessels are decidedly dilated, but further than this there are no alterations. The outer portions of the submucosa are normal.

The remaining coats of the intestine show no change.

EXPERIMENT II. **Dilute sulphuric acid. Duration, twenty-four hours.**

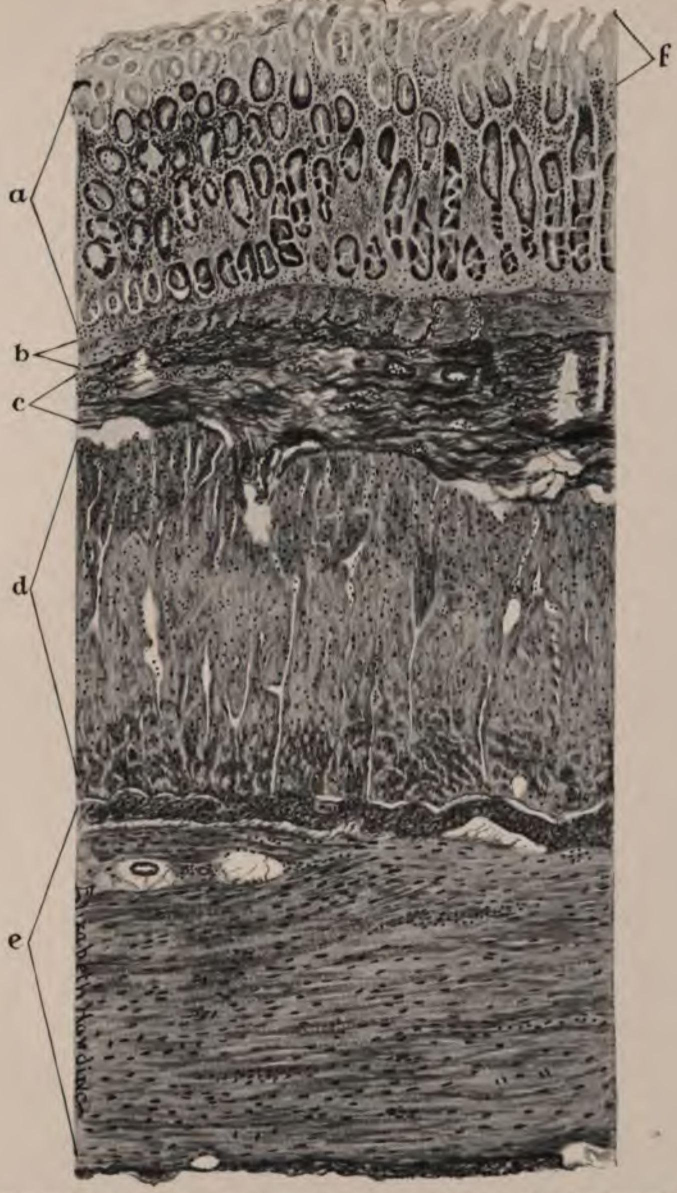
To a dog weighing 7 kg., 10 c.c. of dilute sulphuric acid were administered by the rectum on November 13, 1900; the liquid that was given consisted of 1 part of pure acid to 89 parts of distilled water, this being the dilution necessary to give a solution that will exactly neutralize the liquor potassæ of the U. S. P., volume for volume. Twenty-four hours after the drug was given the animal was killed with chloroform. On examination the mucosa of the large intestine showed slight redness in its lower portions, the change being as usual most marked on the tops of the rugæ; this alteration is not uniform even in the lower part of the bowel.

On microscopic examination with a low power very extensive changes are at once apparent in the mucosa, the muscularis mucosæ, and the submucosa. The surface layer of epithelial cells covering the mucous membrane has been completely destroyed, and the epithelial cells in the mouths and necks of the glands and the structures intervening between them are entirely necrotic. The tissues lying along the surface of the gut are uniformly acidophilic, the nuclei never taking even the most powerful basic stains. These structures are for the most part finely granular, and along the surface, in most situations, do not present any of the morphologic peculiarities that characterize the normal tissues of the parts.

Somewhat deeper down the tissues, while still being practically entirely acidophilic, begin to exhibit in their morphology a certain resemblance to those normally found in the parts. The epithelial cells lining the crypts are swollen, exceedingly irregular in form, and acidophilic throughout, and, although attached to their basement membranes, the coverings of their free ends have in most instances ruptured, and the cellular contents have oftentimes been discharged in irregular masses into the lumina of the crypts. In many of these cells small rounded or oval masses of mucin are found, and it is especially noteworthy that they preserve their form and staining peculiarities, however degenerate the surrounding parts of the cells may be.

Between the crypts in these situations the tissues are considerably swollen, though by no means to such a degree as is often observed in other experimental lesions. The bands of elastic tissue stain fairly well, even for quite a distance into the masses of necrotic material that lie on the surface, and have suffered much less than the neighboring fibres of collagenous tissue. In the dilated lymph spaces there are numerous red blood cells and

PLATE VIII.



Specimen from the lower portion of the large intestine of a dog into which a dilute solution of sulphuric acid had been injected twenty-four hours before the tissues were removed from the animal's body. The specimen was fixed in Bensley's solution and stained by the method of Van Gieson. Beck ¼ inch, Oc. 1 inch. *a.* Mucosa, the outer portion of which (*f*) is entirely necrotic, and deeper down there is much catarrhal change in the glands, and the intervening tissues are swollen, and contain many polymorphonuclear leucocytes and free red blood cells; the polymorphonuclear leucocytes are particularly numerous where the necrotic tissues join those not so much altered. *b.* Swollen muscularis mucosæ, in which there are many polymorphonuclear leucocytes. *c.* Submucosa containing here and there minute collections of polymorphonuclear leucocytes. *d.* Circular muscular layer. *e.* Longitudinal muscular layer. (Exp. II.)

quite a number of polymorphonuclear leucocytes—these in the fresh state, having evidently been surrounded by considerable collections of fluids. These blood cells often stain in a practically normal manner in regions so near the surface that the preexisting structures are entirely degenerate, and it is plain that they were effused into the parts after the maximum deleterious action of the acid had passed away.

Below the areas of actual necrosis the epithelial cells lining the crypts show marked alterations; they are swollen, irregular in form, and have usually shed off from their basement membranes; the nuclei, however, are practically always normal in appearance and stain in the usual way. These cells contain quantities of mucin that is often present as round or oval masses within the cells, or, even more commonly, diffusely scattered throughout their protoplasm. Considerable quantities of free mucin are also found in the lumina of the crypts in these situations. The cells lining the bases of the crypts have likewise shed off from their basement membranes, and are usually swollen and irregular in form, but both their nuclei and their protoplasm stain in the usual manner. Even here mucin formation is frequently observed in the cells, thus indicating that an increased amount of this substance is being produced. Mixed with the shed-off cells there are frequently found collections of polymorphonuclear leucocytes that have evidently made their way through the basement membranes into the lumina of the crypts. The basement membranes of the bodies and bases of the glands appear entirely normal and stain in the usual way.

The interstitial tissues lying between the crypts immediately beneath the area of necrosis show marked alteration. The collagenous fibres are swollen and take their specific stains poorly, while the neighboring elastic tissue fibrils appear in every way normal. The lymph spaces are considerably dilated and are filled with many red cells and multitudes of polymorphonuclear leucocytes; in these situations there are found here and there lymphoid cells and an occasional plasma or connective tissue cell, but the blood cells so largely predominate that they entirely overshadow all other cellular bodies present. It seems probable that the walls of the bloodvessels have been completely destroyed in these areas, as no distinct bloodvessels can be made out. Mucinoblasts are entirely absent from these tissues. Similar changes are observed around the bases of the crypts, the only difference being that the swelling is not so marked and the number of polymorphonuclear leucocytes is somewhat less.

The muscular fibres composing the muscularis mucosæ are very generally more or less separated from each other by fluids that have accumulated between them, and polymorphonuclear leucocytes are very frequently present in the dilated lymph spaces. The muscle fibres composing this layer show no change.

The layer of the submucosa that is immediately beneath the muscularis mucosæ shows considerable alteration. The lymph spaces are dilated, and were evidently filled with fluids in the fresh state; within these spaces small collections of fibrin occasionally occur. In these situations there are found considerable numbers of polymorphonuclear leucocytes, a few lymphoid, plasma, and connective tissue cells; small collections of red blood cells are not infrequently present. The bloodvessels are in many instances dilated, and polymorphonuclear leucocytes are frequently seen collected around and lying attached to their inner coats. Both collagenous and elastic tissues stain in the usual way, and both appear entirely normal. The deeper layers of the submucosa show similar changes, but they are by no means so marked; the tissues of this coat that border upon the circular muscular layer are practically normal. It is a curious fact that the mucinoblasts have entirely disappeared from this layer also.

No changes are found either in the muscular, subserous, or serous coats.

EXPERIMENT III. **Dilute sulphuric acid. Duration, twenty days.**

On December 11, 1900, a dog was given by the rectum 10 c.c. of a solution of sulphuric acid composed of 89 parts of water and 1 part of acid; from this the animal suffered no apparent ill effect. On December 14th the injection was repeated. On the following day the animal was observed to pass much mucus, mixed with blood, and he was evidently quite ill. On December 17th 10 c.c.

of the acid solution were again injected. The dog continued to suffer with diarrhœa, and became so weak that it was thought best not to give another dose of the acid until December 23d, following which he became still weaker. The injection was repeated on December 28th. On December 31st the dog was killed with chloroform, and an autopsy was at once made. The animal was much emaciated, even more so than the one that had received the injections of liquor potassæ on the corresponding dates. On examination no changes were found except in the large intestine; this viscus was entirely empty, and its walls seemed to be about twice the usual thickness. The rugæ on its surface were not so prominent as is usually the case. The mucosa was of a pinkish-gray color, with here and there small spots that were of a light rose-red hue. The appearances are those that would indicate a superficial necrosis of the mucous layer, but there is no evidence of deep ulceration into the wall of the gut.

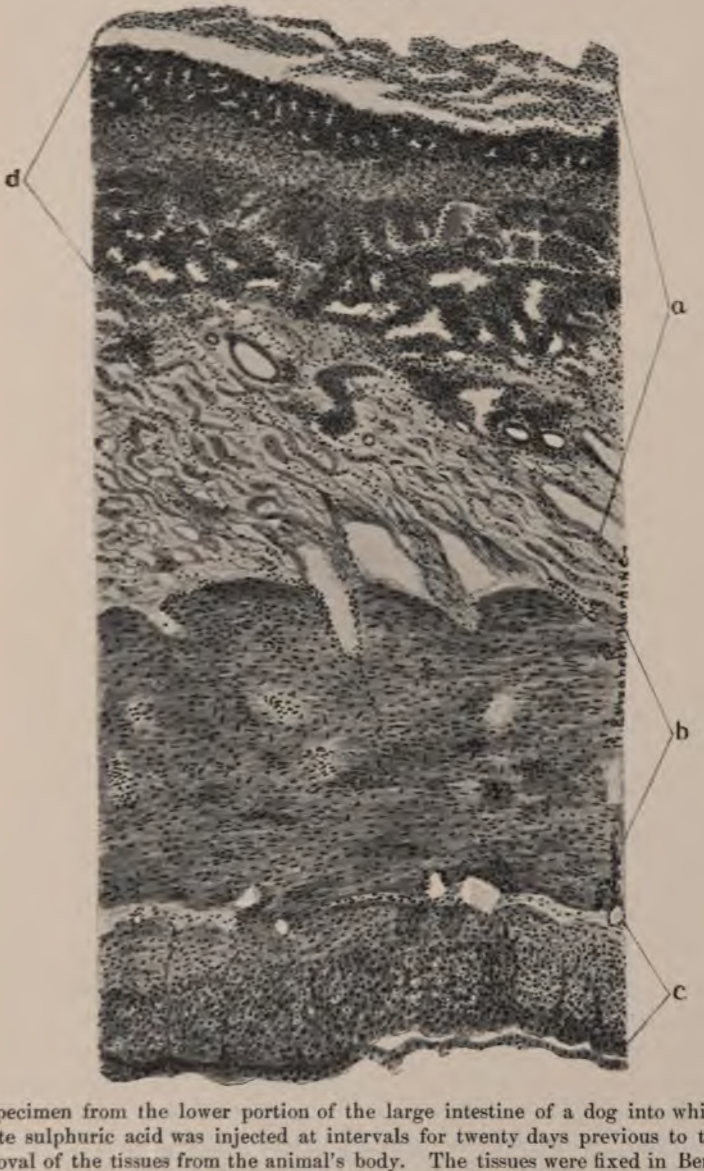
On microscopic examination it was found that the mucosa, in those areas with which the acid came in contact, had entirely sloughed away. The destruction in some cases does not extend below the muscularis mucosæ, but in the majority of instances the pathologic process has gone deeper, and has involved to a greater or less extent the upper layer of the submucosa. In the diseased region the surface of the gut is made up by masses of polymorphonuclear leucocytes, intermingled with which there are found many lymphoid cells and a considerable amount of granular débris. Higher up the gut its surface no longer presents this necrotic change, but the normal mucosa is again found. Where these two areas join the mucous layer begins abruptly. Here the layer of epithelial cells covering the mucosa dips suddenly downward to the ulcerated surface and has made a feeble sort of an effort to grow over it for a short distance; these epithelial cells appear entirely normal except just at the edges of the necrotic areas, where they are somewhat smaller and more irregular in form than is usual. The cells lining the neighboring crypts contain considerable quantities of mucin, but present no other obvious alteration. The tissues lying between the crypts are somewhat swollen, and the bloodvessels are in many instances slightly dilated, but further than this no change is apparent. Underlying the tissues composing the surface of the ulcerated portion of the gut there is an extensive layer containing remnants of the original fibrous structures, a few polymorphonuclear leucocytes and lymphoid cells, and large quantities of fibrin; the fibrin is present to such a degree that in properly stained specimens the tissues appear to be almost entirely made up of this substance. Still deeper down the tissues are much swollen and contain great numbers of plasma cells that very generally are in the process of secreting fibrous tissue; in addition to these there are many lymphoid cells, a few polymorphonuclear leucocytes, and a small number of mucinoblasts. The tissues lying in this area are for the most part entirely degenerate and do not take their specific dyes, but the fibres of white fibrous tissue, although greatly swollen, react to stains in the usual way. The bloodvessels are in most instances dilated, and, near the fibrin layer above referred to, are frequently thrombosed. The muscular walls of these vessels in many instances show practically no alteration, but in others the fibres have lost their identity and have been transformed into solid masses of hyaline material that react strongly to acid stains. Under all conditions, and especially in the latter instances, the elastic tissue fibrils lying in the walls of the vessels show pronounced degenerative change and usually fail to stain. The epithelial cells lining the lymph channels are greatly swollen, and the lumina of these vessels are frequently filled up with desquamated epithelial cells, polymorphonuclear leucocytes, lymphoid cells, and granular débris.

The muscular coats of the gut show comparatively little alteration, but lying between the fibres of the circular muscular layer small collections of polymorphonuclear leucocytes are not uncommonly encountered, and in the fibrous septa between the bundles of the muscle fibres minute groups of lymphoid cells and plasma cells are frequently found. Mucinoblasts are also quite commonly observed in the circular muscular layer.

The longitudinal muscular layer is practically normal.

The subserous and serous coats show no alteration.

PLATE IX.



Specimen from the lower portion of the large intestine of a dog into which dilute sulphuric acid was injected at intervals for twenty days previous to the removal of the tissues from the animal's body. The tissues were fixed in Bensley's solution and stained with hæmalum and eosin. Beck ¼ inch, Oc. 1 inch. *a.* Submucosa, the surface of which is covered by a granular débris, and lower down the tissues contain enormous numbers of polymorphonuclear leucocytes and lymphoid cells (*d*). *b.* Circular muscular layer. *c.* Longitudinal muscular layer. (Exp. III.)

EXPERIMENT IV. **Dilute nitric acid. Duration, twenty-four hours.**

On January 7, 1901, there were injected into the rectum of a dog 10 c.c. of a watery solution of nitric acid that corresponded in strength to the sulphuric acid solution employed in Experiments II. and III. In exactly twenty-four hours the animal was killed with chloroform, and an autopsy was at once made. When the large intestine was opened its upper half was found to contain fecal matter; the lower portion was practically empty. The walls of the lower half of the gut were swollen and the rugæ were much less prominent than usual. In this situation the mucosa was pinkish-gray in color, with here and there small areas that were decidedly redder than the surrounding parts. At a point about three inches from the rectum, which corresponds to the place where the end of the syringe rested while the injections were being made, the mucosa was evidently necrotic and presented the appearance of superficial ulceration.

On microscopic examination it is found that in those areas where the acid came directly in contact with the mucosa the upper layer of this coat is entirely necrotic, and is beginning to slough off in many situations. With the exception that the superficial layer of the epithelial cells is here absent, the different morphologic elements that go to make up the mucous layer are found to be present, and occupy the relative position in which they occur in health. The epithelial cells in the mouths and necks of the crypts have entirely disintegrated, and the granular débris that results stains uniformly with acid dyes. However, scattered through these masses, particles of mucin are not uncommonly encountered that in some instances often preserve their normal form, and in all cases stain in the usual way. Somewhat lower down, but still within the mass of necrotic tissue, the epithelial cells do not show such marked evidences of degenerative change, but even here their outlines are ill-defined, the cells appear shorter than normal, and their nuclei often fail to stain; the mucin particles within the cells show no alteration in either form or staining reactions. The elastic tissue basement membranes surrounding the crypts are fairly well-preserved, and stain in many instances outward to the free ends of the crypts. In the superficial portions of the sloughing tissues the interstitial structures are totally acidophilic, but even here swollen bands of collagenous tissue may be readily made out. Between the crypts in the lower portion of these masses there are multitudes of polymorphonuclear leucocytes, these occurring in such numbers that they practically replace all other tissues that were previously present, and push the bodies of the crypts widely apart.

Frequently the necrotic portions of the mucosa still remain attached to the more or less normal tissues that lie beneath, but under these circumstances the changes occurring in the dead tissues are in every way similar to those just described.

The only parts of the mucous layer that retain in any way their normal peculiarities are the basal portions of the glands and the intervening structures, but even here the epithelial cells are usually swollen and irregular in form, and quantities of them have desquamated in all instances and lie loosely in the lumina of the crypts. Intermingled with these shed-off epithelial cells there are also numerous polymorphonuclear leucocytes, these being present in such numbers oftentimes that they completely fill the lumina of the crypts. Neither the polymorphonuclear leucocytes nor the epithelial cells, however, show any alteration in their staining peculiarities. The basement membranes of the crypts stain in the usual way.

The tissues that lie between the lower portions of the crypts and around their bases are very greatly swollen and contain, in addition to the fluids that were evidently present to a considerable extent, great numbers of polymorphonuclear leucocytes, a few mucinoblasts, and a few plasma cells. Occasionally dilated bloodvessels are found in these areas, but they are by no means commonly present. In some instances they have evidently ruptured, and under these circumstances small hemorrhages are found in the surrounding tissues. The collagenous tissues are fairly well-preserved, though the fibrils usually appear slightly swollen.

The outer layers of the muscularis mucosæ are somewhat swollen, and there are numerous polymorphonuclear leucocytes lying between the muscle fibres.

The deeper portions of this coat are practically normal.

The submucosa shows no change with the exception that the bloodvessels, especially those lying immediately beneath the muscularis mucosæ, are greatly dilated and are filled with blood; around these bloodvessels a few polymorphonuclear leucocytes are sometimes found.

The other coats of the intestine are entirely normal.

EXPERIMENT V. **Dilute acetic acid. Duration, twenty-four hours.**

Ten c.c. of a solution of acetic acid, corresponding in strength to the acid solutions used in Experiments II., III., and IV., were injected into the large intestine of a dog on January 18, 1901. Twenty-four hours later the animal was killed with chloroform, and an atuopsy was at once made. On examination the large intestine was found to be filled with fecal matter. The walls of the lower half of the gut were swollen and the mucosa was quite red. The rugæ were numerous and prominent; the mucosa covering these elevations was no redder than the neighboring surface of the bowel.

On microscopic examination it is found that the superficial layer of surface epithelium has been completely eroded away in those parts with which the acid came in direct contact, and in some situations the tissues immediately beneath have likewise become necrotic and have sloughed away. The necrosis has in some situations extended down into the necks of the crypts, but in most instances the process has only involved the epithelial cells lying at the margins of the mouths of the glands. However, more or less alteration is always found in the cells in these situations, for they are swollen, irregular in form, and their protoplasm is decidedly granular; in many instances they have shed off from their basement membranes. These changes sometimes extend downward into the necks of the crypts, but never go deeper, the cells lining the bodies and bases of the glands being entirely normal. No mucin is found in any of the diseased epithelial cells, and this substance is evidently being produced in much smaller quantities than normal in the tissues that lie beneath, they containing only here and there traces within their protoplasm. The elastic tissue basement membranes upon which the diseased epithelial cells lie appear and stain in a perfectly normal manner.

The tissues intervening between the mouths and necks of the glands are greatly swollen, this being due to enormous dilatation of the smaller bloodvessels lying in the parts, to the accumulation of quantities of fluids in the tissues, and likewise to the presence of many polymorphonuclear leucocytes; in addition to the above-named cellular elements, a few lymphoid and a small number of plasma cells are present. Mucinoblasts are never observed in the diseased tissues. The collagenous and elastic tissue fibrils stain in a perfectly normal manner, even where the alterations are most pronounced. Changes similar to those just described, though much less marked, are found in the tissues intervening between the bodies of the crypts and occasionally even so low down as between and beneath the bases of these glands; on the whole, however, the alterations may be said to be confined to the upper half of the mucosa.

No changes are found in any of the other coats of the intestine.

Résumé of the Changes Resulting from Acids.

Dilute sulphuric acid. Very acute. (Twelve hours.) At the post-mortem examination the mucosa of the lower half of the large intestine was found considerably reddened and its walls were decidedly swollen.

Microscopic examination shows that the superficial epithelium has entirely desquamated, and that the cells of the mouths and necks of the crypts exhibit catarrhal alteration. In some instances these changes extend down into the bodies of the glands. Between the epithelial cells in the deeper portions of the crypts there are quite a number of polymorphonuclear leucocytes; in some instances these have collected in considerable numbers in the lumina of the crypts. The interglandular tissues are considerably swollen as a result of the effused blood, and polymorphonuclear leucocytes have migrated into the part in great numbers.

The muscularis mucosæ is somewhat swollen. In the interspaces of the tissues there are here and there quite a number of polymorphonuclear leucocytes.

The layer of the submucosa lying next to the muscularis mucosæ contains numerous dilated bloodvessels. There are many polymorphonuclear leucocytes in the interspaces of these tissues.

Dilute sulphuric acid. Acute. (Twenty-four hours.) On post-mortem examination the lower half of the intestine was found decidedly reddened.

On microscopic examination the epithelium that covered the surface of the mucosa and that that lined the mouths and necks of the crypts is found absent. The interglandular tissues immediately along the surface are entirely necrotic. The epithelial cells in the bodies of the crypts show decided catarrhal change. Polymorphonuclear leucocytes have frequently penetrated between these cells and lie in considerable numbers in the lumina of the crypts. The interglandular tissues are here greatly swollen as a result of the presence of much hemorrhage and of great numbers of polymorphonuclear leucocytes. The pre-existing structures, with the exception of the elastic tissue fibrils, have entirely disappeared in these situations. In the bases of the crypts the epithelial cells are sometimes catarrhal, and there is much mucin formation going on within them.

The muscularis mucosæ is swollen and contains in its interspaces numerous polymorphonuclear leucocytes.

The more superficial layers of the submucosa are swollen as a result of the presence of fluids and of great numbers of polymorphonuclear leucocytes.

Dilute nitric acid. Acute. (Twenty-four hours.) The mucosa of the lower half of the large intestine was found to be reddened and at some points necrotic on post-mortem examination. In the same situations the walls of the gut were distinctly swollen.

On microscopic examination the epithelium that lined the surface of the intestine and that that covered the mouths and necks of the glands is found to have entirely desquamated. The interglandular substance at these points is entirely necrotic. In the deeper portion of the necrotic tissues there are multitudes of polymorphonuclear leucocytes.

In the basal portions of the glands the epithelial cells have universally desquamated, but preserve their form and staining reaction in an almost normal way. Intermingled with these cells there are great numbers of polymorphonuclear leucocytes. The interglandular tissues of the basal portions of the crypts are much swollen; this is the result of the presence of great quantities of liquids and quite an amount of hemorrhage. Polymorphonuclear leucocytes are abundantly present in these tissues. The pre-existing collagenous tissues stain very poorly, but the elastin presents practically no alteration.

The muscularis mucosæ is swollen. Between its fibrils there are numerous polymorphonuclear leucocytes.

The bloodvessels of the more superficial portions of the submucosa are considerably dilated, and the interspaces of the tissues contain numerous polymorphonuclear leucocytes.

Dilute acetic acid. Acute. (Twenty-four hours.) At the autopsy the lower half of the large intestine was found to be swollen and its mucosa somewhat reddened.

The epithelial cells that covered the surface of the intestine have entirely shed off, and those that normally line the mouths and necks of the crypts have in some instances undergone a similar change. The cells in the lower portions of the crypts are entirely normal. The elastic tissue basement membranes are in all situations normal. The interglandular tissues are considerably swollen as a result of the dilatation of the bloodvessels of the part and of the accumulations in the lymph spaces of great quantities of fluids. These structures contain enormous numbers of polymorphonuclear leucocytes. The pre-existing collagenous and elastic tissues stain normally. These changes are confined almost entirely to the outer half of the mucosa, there being but little alteration in the deeper portion of this coat.

Dilute sulphuric acid. Chronic. (Twenty days.) Some time before the dog died he became considerably emaciated. At the autopsy the walls of the lower half of the large intestine were found to be considerably thickened, and the mucous surface was of a pinkish-gray color, with red spots scattered here and there upon its surface.

On microscopic examination the mucosa is found to be entirely absent, and the ulceration has extended in many instances even through the muscularis mucosæ. The surface of these ulcers consists of a granular débris, intermingled with which many polymorphonuclear leucocytes and lymphoid cells are found. Specimens were examined at the point where the diseased part of the bowel joined the normal portion that lay in the upper part of the gut. It was found that the lesions at this point begin abruptly, and that epithelial cells have grown down from the normal mucosa over the edges of the ulcerated surface. Beneath the floors of the ulcers there are the remains of the original tissues of the part, intermingled with which there are many polymorphonuclear leucocytes and lymphoid cells and an enormous amount of fibrin. At some distance below the surface of the ulcers there are great numbers of plasma cells, and, as a consequence, much fibrous tissue is being formed in these parts. The vessels lying in the tissues below the surface of the ulcers are dilated and are often thrombosed. The walls of many of these vessels are hyaline.

CHAPTER IV.

EXPERIMENTS TO DETERMINE THE EFFECTS PRODUCED ON THE LARGE INTESTINES OF DOGS BY THE INJECTION OF SOLUTIONS OF NITRATE OF SILVER.

EXPERIMENT I. **Ten per cent. solution of nitrate of silver. Duration, twenty-four hours.**

ON February 6, 1901, 10 c.c. of a 10 per cent. solution of silver nitrate were injected into the large intestine of a medium-sized dog, he having previously received a large dose of morphine. Following the injection the animal exhibited no evidence of illness, but as he was killed just twenty-four hours after the drug was administered it was quite possible that the morphine prevented the development of the usual symptoms that result when the intestinal mucosa is subjected to irritation.

On post-mortem examination the lower half of the large intestine was found to contain a small quantity of fecal matter, and the mucosa covering this part of the bowel was uniformly quite red. The transverse rugæ were prominent in this situation, but their apices appeared no redder than the surrounding surfaces. There were at no points evidence of ulceration.

On microscopic examination the superficial layer of epithelium that covered the mucous surface in health was found to be eroded in the regions most affected, and along the surface of the mucosa there were found many swollen cells and much granular detritus. The epithelial cells that lined the mouths of the crypts show a marked catarrhal change, they being swollen, irregular in form, and have in most instances desquamated. It is noteworthy that these cells contain no mucin, and neither is this substance found in any part of the glands or on the surface of the intestine in the area most affected. The cells in the necks of the crypts are oftentimes swollen and have frequently shed off from their basement membranes, though these changes are by no means so marked as are found in the mouths of the glands. The epithelial cells lining the bodies of the crypts show slight catarrhal changes in some instances, but, further than this, and that they never contain mucin, no further alterations are observed. The epithelium lining the bases of the crypts show no change. It should be noted that the lumina of the crypts in these situations are always much diminished, owing to the fact that the exudate in the surrounding interglandular substance has frequently caused considerable compression of the crypts, they being in many instances not more than 30μ from basement membrane to basement membrane in diameter. The basement membranes of the crypts do not stain well toward the free surface of the bowel, but deeper down around the basal portions of the crypts they show but little change.

The free surface of the interglandular tissues that have been denuded as a result of the shedding off of the surface epithelium shows slight evidence of necrotic change. The cells that lay in these situations have generally become necrotic, and the collagenous tissue fibrils are swollen and are oftentimes granular; these structures take the acid stains with much intensity. Immediately beneath the surface the interglandular tissues are very greatly swollen as a result of the accumulation of much fluid in the parts, from numerous hemorrhages, and in a considerable degree as an outcome of the emigration into the parts of multitudes of polymorphonuclear leucocytes. As would naturally be expected, the bloodvessels are also much dilated and are distended with blood. In addition to these extraneous substances there are the usual number of lymphoid cells and many pseudoplasma cells, the latter appearing to be present in greater numbers than is usual in health. It is noteworthy that mucinoblasts have entirely disappeared from the tissues most affected. While these changes are most pronounced toward the free surface of the mucosa, they show but little diminution in intensity as the deeper portions of this layer are approached, the alterations being almost as severe around the basal portions of the crypts as in the more superficial portions. It should also be noted that changes of a similar kind, though not quite so intense, are present between the crypts in many situations where the epithelial structures covering the surface of the gut and those lining the crypts have practically remained entirely normal. It would therefore seem that nitrate of silver or the acid that results from its decomposition is absorbed into the deeper tissues, where its greatest action is exerted.

The fibres of the muscularis mucosæ appear normal, though they are universally separated from each other by more or less fluid in which there are often polymorphonuclear leucocytes. The coat, as a whole, is therefore decidedly thickened. The elastic tissue network of this layer seems to have suffered no change.

The submucosa is decidedly thickened beneath those areas where the changes in the mucosa are most marked, this being due to the accumulation of liquids in the parts, to the dilatation of the bloodvessels, and to the presence in the tissues of great numbers of polymorphonuclear leucocytes. There are also found many more than the usual number of lymphoid cells in these tissues, but the mucinoblasts have entirely disappeared. The bands of collagenous tissues, especially those lying next to the submucosa, are distinctly swollen and appear somewhat granular, and the elastic tissues do not take their specific stains with quite the usual intensity. The connective tissue cells seem to have entirely disappeared. The number of dilated bloodvessels in this layer is much greater than the writer has ever observed in any other experimental lesion of the intestine; the vessels are invariably filled with blood. The lymph nodes—which are very frequent in the submucosa—are distinctly swollen, their bloodvessels are dilated, and they contain in addition to an increased number of lymphoid cells a great many polymorphonuclear leucocytes.

Notwithstanding that the changes are so marked in the submucosa, further than here and there a slight dilatation of the vessels, no changes are observed in the muscular coats.

The subserous and serous coats are normal.

EXPERIMENT II. **Dilute solution of silver nitrate. Duration, eighteen days.**

On February 6, 1901, 2 c.c. of a 10 per cent. aqueous solution of nitrate of silver were injected into the rectum of a rather large dog. The injections were repeated on the 8th, 10th, 12th, 14th, 16th, 18th, 20th, and 22d of February. During this period the dog remained apparently healthy, with the exception only that the stools, which were not particularly numerous, contained more or less bloody mucus. On February 24, 1901, the animal was killed with chloroform, and an autopsy was at once made.

The mucosa of the lower half of the large intestine was found to be somewhat redder than normal, with here and there over its surface bright blood-red spots. The transverse rugæ were quite numerous in the area showing the most marked change, but the mucosa covering the apices of these elevations was no redder than that surrounding. The walls of the gut were decidedly swollen in the affected region.

On microscopic examination it is found that the epithelial structures of the mucosa of the intestine have suffered comparatively little, but there are most pronounced changes in the interglandular tissues of the sections examined. Although the epithelial cells show no marked alteration, it is universally the case that they stain somewhat more intensely with basic dyes than is usual, and there are within their protoplasm no structures that react in a frank manner to the specific stains for mucin; with Mayer's muchæmatein the cells sometimes stain throughout of a reddish-purple color; but, while there is a suggestion of mucin in the tint imparted to them, the reaction is not so pronounced as to warrant the assertion that they really contain this substance. The changes in the interstitial substance consist in a dilatation of the lymphatics of the tissues, this occurring in an especially marked manner near the surface of the mucosa, and the accumulation in the parts of enormous numbers of plasma cells; there are, in addition, a few polymorphonuclear leucocytes, quite a number of lymphoid cells, and many mucinoblasts. In the regions where the swelling is most marked the collagenous tissue fibrils are distinctly swollen and take the stain very poorly. On the other hand, the elastic tissues appear to be in every particular normal. Around the basal portions of the crypts mucin is frequently present in considerable quantity; it lies loosely in the tissues, and probably is the result of the disintegration of the mucinoblasts that are very numerous in these areas. The bloodvessels of the interglandular substance shows comparatively no change.

The muscularis mucosæ is decidedly swollen, its fibres often appear somewhat larger than usual, and their protoplasm is distinctly granular. Between the muscle fibres there are a few polymorphonuclear leucocytes and lymphoid cells in addition to the fluid that is present in the lymph spaces in considerable quantity.

The layers of the submucosa lying next to the muscularis mucosæ contain numerous plasma cells, and there appears to be a certain amount of fibrous tissue formation going on in this region. There are also in these tissues great numbers of large mucinoblasts, and here and there are found small collections of polymorphonuclear leucocytes and lymphoid cells.

As the circular muscular coat is approached the changes become less and less pronounced until those tissues that lie in contact with this layer appear perfectly normal. The bloodvessels of the submucosa present no alterations, with the exception that their muscular walls appear swollen and the fibres granular.

No changes are observed in either the circular or longitudinal muscular coats other than that the fibres composing these layers appear granular, and their outlines are ill-defined. The elastic tissue stroma of these coats, however, presents no alteration.

The subserous and serous coats show no change.

In some situations the alterations have been more pronounced; the epithelial cells lining the surface of the mucosa have shed off and there are slight catarrhal changes in the mouths of the crypts. The interglandular substance and deeper coats of the bowel present appearances in every way similar to those that have just been described as occurring more generally, though it is possible that the changes in the former instances may be somewhat more severe. It is noteworthy that where the superficial epithelial layer has desquamated the interglandular substance lying beneath has appeared in a measure to collapse, this doubtless being due to the fact that under these circumstances the fluids that were contained in the part have found ready exit onto the free surface of the intestine.

In some situations the mucosa has suffered even more greatly, and a large part of its substance has sloughed away. These alterations, however, must have resulted from some of the earlier injections, for reparative changes have gone on to a considerable degree in the areas involved. Over the parts affected a new coating of epithelial cells has grown; these cells are fairly well-developed and exhibit in their histology the peculiarities that characterize ordinary surface epithelium, with the exception only that they never contain mucin. They do not lie upon a basement membrane, but are in direct contact with the tissues beneath. There are here and there vestiges of the original glandular structures of the parts remaining; these remnants of the glands are, as would be expected, not so tall as the crypts found in the normal mucosa, but their circumference is often two or three times as great. In some cases the openings of these crypts appear to have been occluded, and there have resulted cystic dilatations of the glands; the contents of these cysts consist of desquamated epithelial cells and granular débris in which no mucin is found. It may be remarked, however, that the epithelial cells lining both the cysts and the dilated crypts do not, as a rule, present any evidences of catarrhal change, but they stain somewhat more deeply than do the cells in health. Between these distorted crypts there is an interglandular substance composed of newly-formed fibrous tissue, in the interspaces of which there are enormous numbers of plasma cells, many lymphoid cells and mucinoblasts, and a few polymorphonuclear leucocytes; red blood-corpuscles are sometimes found lying loosely in these tissues, this having evidently resulted from the rupture of the embryonic bloodvessels that have penetrated the parts.

Beneath these areas the muscularis mucosæ, submucosa, and circular muscular coats present changes in every way similar to those that occur in other parts of the diseased intestine.

From the foregoing it is apparent that the changes produced by nitrate of silver resemble very closely those caused by nitric acid.

Résumé of the Changes Produced by Nitrate of Silver.

Acute. (**Twenty-four hours.**) At the necropsy the mucosa of the lower part of the large intestine was found to be decidedly reddened; there were many transverse rugæ in this part of the intestine. On microscopic examination it is found that the epithelial cells that lined the surface of the gut and those that lay in the mouths and necks of the crypts have entirely shed off. In the lower portion of the crypts the cells are swollen, irregular in form, and have sometimes desquamated, but the changes are by no means so pronounced as nearer the surface. It is noteworthy that mucin formation seems to have ceased in these cells entirely.

The crypts are somewhat smaller than usual, owing to the accumulation of inflammatory materials in the surrounding tissues.

The interglandular tissues contain a great amount of hemorrhage, and the parts are swollen as a result of the presence of much fluid. A great many polymorphonuclear leucocytes are found in these tissues. These alterations extend to the basal portions of the crypts, but diminish gradually as this part of the mucosa is approached.

The muscularis mucosæ is swollen and there are quite a number of polymorphonuclear leucocytes lying between its fibres.

The layer of the submucosa lying next to the muscularis mucosæ contains considerable numbers of polymorphonuclear leucocytes, and the bloodvessels in this part of the intestinal wall are considerably dilated.

Chronic. (**Eighteen days.**) At the post-mortem examination the intestine was found to be considerably swollen and its mucous surface was decidedly reddened; here and there over the mucosa there are bright blood-red spots.

On microscopic examination the changes in the intestine are found to vary very much in different situations. For the most part the epithelial coverings of the intestine have suffered no alteration other than that the cells seem to secrete less mucin than is normally the case, and they stain more intensely with basic dyes than usual. Notwithstanding that there are practically no changes in the epithelial lining of the intestine, the interglandular tissues show marked alteration. The lymphatic vessels are distended with fluids, and there have accumulated in the parts enormous numbers of plasma cells. The collagenous tissues stain rather poorly, but the elastin shows no alteration. It is noteworthy that mucin is found in appreciable quantity in the tissues around the basal portions of the glands. The muscularis mucosæ is somewhat swollen, and between its fibres there are a few polymorphonuclear leucocytes and lymphoid cells.

In other situations pronounced catarrhal changes are found;

the epithelial cells lining the surface of the intestine and those covering the mouths of the crypts have entirely shed off, but the alterations in the interglandular substance, though perhaps somewhat more intense, are in every way similar to those that occur where the changes on the surface are not so pronounced.

Here and there on the mucous surface there are well-defined ulcers; these extend to varying depths into the substance of the mucosa, sometimes even completely through this layer down to the muscularis mucosæ. When there are remnants of the crypts still in the parts the epithelial cells lining them show surprisingly little catarrhal change; these cells never contain mucin. Between the partially destroyed crypts, and forming the bases of the ulcers, there is much newly-formed fibrous tissue; as might be expected, there are between the fibrils of this tissue great numbers of plasma cells and many lymphoid cells. The surface of these ulcers is not uncommonly covered over by well-developed, newly-formed epithelium.

CHAPTER V.

EXPERIMENTS TO DETERMINE THE EFFECTS OF COLCHICUM IN POISONOUS DOSES ON THE LARGE INTESTINES OF DOGS.

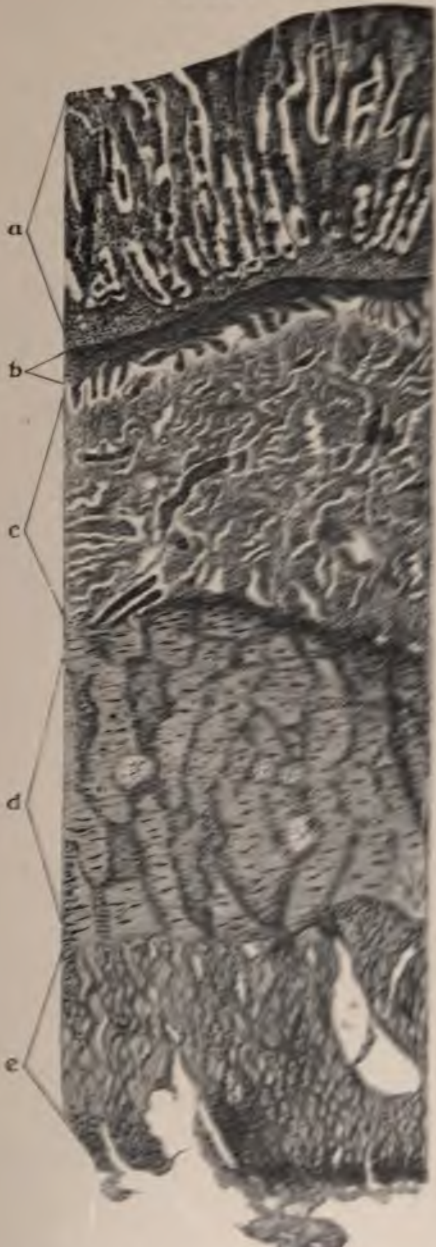
EXPERIMENT I. **Duration, probably about twelve hours.**

A DOG weighing about 7 kg. was given 25 c.c. of the fluid extract of colchicum seed at 5.30 P.M., October 18, 1900. At an early hour on the following morning he was found dead.

A post-mortem was at once made, with the following results: The intestinal tract shows but little change, there being only a few hemorrhagic areas on the inner surface of the stomach and several dark bluish-red discolorations on the mucosa of the lower part of the large intestine. These discolorations occur on the tops of the rugæ principally, but the change also extends to the mucosa that lies between them to a certain extent. The affected area shows no swelling. The entire gastro-intestinal tract is empty.

On microscopic examination most exquisite and extensive catarrhal alterations are found in the mucosa of the intestine. Along its free surface there are numerous thick masses of mucin in which there are found many epithelial cells that universally show degenerative changes; there is quite an amount of granular dêbris also intermixed with this mucin, and many bacteria are present. On close inspection it is found that the surface layer of epithelium is at all points absent, and throughout the crypts most extensive catarrhal changes are apparent. The epithelial cells that lie in the mouths and necks of the crypts are swollen, irregular in form, and, for the most part, have been loosened from their basement membranes; they very generally contain quantities of mucin. In some cases these cells have undergone such extensive changes that masses of partially broken up cells and granular detritus fill the lumina of the glands. Lower down in the bodies of the glands similar alterations also occur, though the

PLATE X.



The specimen is from about the middle portion of the large intestine of a dog that had been given by the mouth 25 c.c. of extract of colchicum probably about twelve hours before death occurred. The tissues were fixed in Bensley's solution and stained with carbol toluidin-blue and eosin. Beck ¼ inch, Oc. 1 inch. *a.* Mucosa, showing extensive catarrhal change in the epithelial cells of the surface and of the crypts and swelling of the intervening tissues. *b.* Muscularis mucosæ. *c.* Submucosa. *d.* Circular muscular layer. *e.* Longitudinal muscular layer. (Exp. I.)

cells do not show quite the same degree of change that they exhibit near the free ends of the crypts; these cells show, almost without exception, mucin within their protoplasm. It is noteworthy that the tissues intervening between the necks of the glands are swollen to such an extent that the lumina of these structures are often nearly and sometimes entirely closed at the point where they open upon the surface of the intestine.

The elastic tissue that constitutes the basement membranes of the crypts fails to stain in its outer two-thirds, but that upon which the cells in the bodies of the glands rest is entirely unaltered.

Marked degenerative changes have occurred on the surface of the tissues that lie between the crypts; the cells in these situations are very granular, in most cases have lost their nuclei, and all of the contained structures are, as a rule, decidedly acidophilic. Between many of the glands and just beneath the surface there are hemorrhages, which are often extensive, so much so that they completely mask the tissue in which they lie, and, as before remarked, encroach upon the crypts to such a degree that their lumina are completely obliterated. In those areas where no hemorrhages have occurred there is always marked swelling. The cells lying in the swollen tissues usually show evidence of degenerative change, they being quite often decidedly acidophilic, and their nuclei frequently show fragmentation. The blood cells that lie in the hemorrhagic areas likewise show degenerative changes; the hæmoglobin is more or less dissolved from the cells, and in quite a number of instances they seem to be in a measure amalgamated together, forming almost homogeneous acidophilic masses. Lower down between the crypts the tissues quite frequently show a slight degree of swelling, but no hemorrhages or marked degenerative changes are to be observed. Throughout the tissues that intervene between the crypts there are numerous, unusually large mucinoblasts. These cells, as a rule, lie just beneath the basement membrane; in some instances they have penetrated through this coat and lie partially or wholly within the lumina of the crypts. These mucinoblasts are breaking up to a marked degree, as free granules that plainly belong to the matured cells are frequently found in the tissues.

The muscularis mucosæ, the submucosa, the muscular coats, and the serous covering of the intestine are entirely normal.

EXPERIMENT II. **Duration, probably about fifty-six hours.**

To a dog weighing 8 kg., 12 c.c. of the fluid extract of colchicum seed were given by means of a stomach-tube. On the following day the dog suffered with profuse watery stools, mixed with blood, and the animal was evidently quite weak. After thirty-six hours from the time that the drug was given the dog was much better, and the diarrhœa seemed to have subsided. Six hours later an equal quantity of the fluid extract of colchicum was again administered, and the animal died some time during the ensuing night. Death resulted in from fifty-four to sixty hours after the first dose was given. As soon as the animal was found dead a post-mortem was made and the following observations recorded :

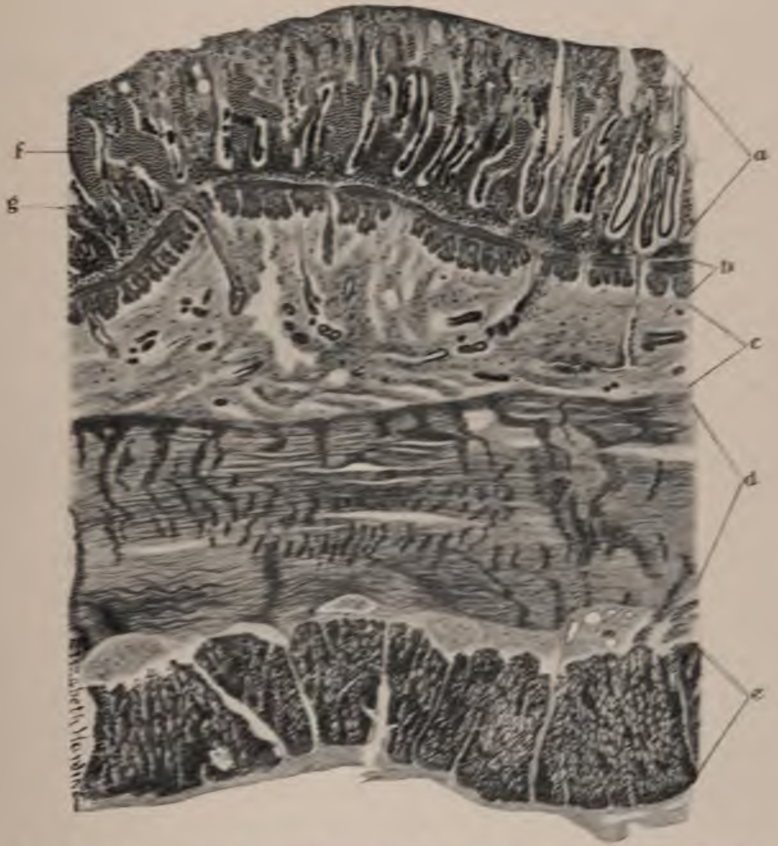
The mucosa of the entire intestinal tract is greatly reddened, the intensity of the process diminishing from above downward. The large intestine is empty and its mucous surface is very red. The apices of the rugæ are distinctly redder than the neighboring mucosa. There is nowhere any appearance of ulceration.

Macroscopic examination of the sections prepared for microscopic examination show no change. On examining the mucosa with a low power most marked alterations are at once apparent. The entire layer of surface epithelium is absent, and in its place a coat of granular dêbris is found ; the free surface of the layer of granular material is very smooth and uniform and does not exhibit those minute elevations and depressions that are seen on the normal mucosa. This material is almost uniformly acidophilic, there being only here and there cells with nuclei that still take the basic stain feebly. It is largely composed of red blood-corpuscles in varying stages of disintegration ; hæmoglobin has been dissolved out of many of the cells to such an extent that they present the appearance of the so-called " phantom corpuscles" sometimes observed in the urine. Intermingled with these disintegrating red cells there are a few partially broken-up lymphoid cells. There are also quite a number of necrotic epithelial cells, but they are distinguished only by their positions, since they have all lost the characteristics of the normal cells. At some points small particles of mucus are found, but the amount of this substance is very small. Throughout this material there are varying numbers of bacteria. Immediately beneath this granular layer, but separated from it by no well-marked line of demarcation, are the tissues of the mucosa. Where in contact with the granular material the tissues are universally acidophilic, and are evidently completely necrotic, but they still preserve enough of their morphologic peculiarities to permit recognition. Passing down into the mucosa the necrotic tissues gradually give way to more or less normal structures. In these situations the epithelial cells of the crypts show everywhere marked degenerative changes, but notwithstanding this present a certain degree of resemblance to the normal cells in their morphologic and staining peculiarities. These cells lie singly or, much more commonly, in clumps. When examined with high powers it is found that they are exceedingly irregular in form, some being spindle-shaped, others oval, and still others rounded; the rounded ones are especially common. In some situations they present a very irregular appearance, which is evidently the result of necrotic changes in and subsequent rupture of the capsules of the cells. The protoplasm of the cells is generally acidophilic, though in many instances the entire cell is so intensely basophilic that it is impossible to make out the nucleus. With high powers the protoplasm of all the cells appear granular, but this is much more marked in the cells the protoplasm of which still exhibits more or less affinity for basic dyes. Many of the cells contain small vacuoles. Small granules of mucin are frequently present within the protoplasm of these cells. A great number of the cells have lost their nuclei, and even in those in which the nuclei are still perceptible they, as a rule, exhibit alterations. The nuclei often lie at the sides of the cells, and either stain very poorly or with unusual intensity. In the former case they preserve their form and usual size and even exhibit poorly stained but still quite distinct particles of chromatin arranged around the inner borders of the nuclear membranes; in these cases the nucleoli are usually very distinct. These cells commonly contain granules that give the mucin reaction. The cells with deeply staining nuclei are not so numerous as those just described, are rounded or oblong in form, and they are usually crowded together in the centres of the lumina of the crypts. The protoplasm of these cells is more intensely acidophilic and decidedly more homogeneous than that of the cells with the faintly staining nuclei. Within their protoplasm small granules are sometimes present, but not so often as in the other cells. The nuclei are smaller than those of the cells first described, measuring usually about 3.5μ in diameter. They are unusually rounded, but are often oblong or irregular in form, and sometimes appear to be fragmented. These nuclei stain intensely with all nuclear dyes, and appear almost homogeneous throughout. They contain no nucleoli. In sections stained in some ways there are often seen pale, rounded areas surrounding these masses of chromatin, the nuclear membrane being under these circumstances entirely absent. The foregoing description applies to the necks of the crypts

Deeper down in the bodies of the glands the condition of the epithelium is in general much the same as nearer the surface. Indeed, it may be said that there is no difference other than one of degree. The epithelial cells are invariably loosened from their basement membranes, but not infrequently remain attached to each other in the same relative positions as in health. Under these circumstances the protoplasm is not quite so basophilic as that of the normal cells, and the nuclei stain somewhat feebly, but the cells are otherwise normal. Internal to this layer of cells, and usually entirely filling the lumina of the crypts, are masses of cells with strongly marked acidophilic protoplasm and deeply staining nuclei, such as have been described in speaking of the changes in the necks of the glands. These cells do not contain mucin granules so often as those that lie in the necks of the crypts, but enough of this substance is present to make it quite conspicuous in properly stained sections. There is also much free mucus among the cells. This mucin formation is of considerable interest, since it is rarely elaborated in the bodies of the glands in health.

The elastic tissue composing the basement membranes upon which the epithelial cells rest is not greatly altered except along the free surface of the intestine, where, as the result of the superficial ulceration, it has entirely disappeared. In the upper portion

PLATE XI.



Specimen from about the middle portion of the large intestine of a dog that had received 12 c.c. of the fluid extract of colchicum about fifty-six hours and a like quantity about twelve hours before death occurred. The tissues were fixed in Bensley's solution and stained with haemalum and eosin. Beck ⅙ inch, Oc. 1 inch. *a*. Mucosa, showing necrosis of its free surface, desquamation of the epithelial cells of the lower portions of the crypts (*g*), and hemorrhages into the intervening tissues (*f*). *b*. Muscularis mucosæ. *c*. Submucosa. *d*. Circular muscular layer. *e*. Longitudinal muscular layer. (Exp. II.)

of the crypts it does not stain well, but lower down no alteration is, as a rule, apparent. It is noteworthy that the neighboring fibres of collagenous tissue are better preserved than those composed of elastin.

Between the crypts marked alterations are observed. The tissues are greatly swollen as a result of the increase in the cellular constituents of the parts, collection of fluid in the lymphatics, and enormous dilatation of the bloodvessels. On the free surface of the intestine, and extending downward for a considerable distance, the tissues are in a state of necrosis; the nuclei no longer take the basic stain, but, along with the other structures, exhibit acidophilic affinities. Into this mass of broken-down tissue the dilated bloodvessels extend, and their walls also becoming necrotic and giving way, the blood is poured directly into the diseased areas; as a consequence of this a great many red blood cells are found in these situations. These dilated bloodvessels are most numerous in the convex portions of the rugæ. From the necrotic tissues it is obvious that the blood can easily find its way to the free surface of the intestine, where, as already mentioned, it is present in considerable quantities.

Passing downward toward the muscularis mucosæ the necrotic changes become less and less marked, but do not entirely cease until this coat is reached; around the bases of the crypts the change is very slight. Between the crypts numerous cells are found in the tissues; for the most part these are the larger phagocytes of Metschnikoff (epithelioid cells), but mixed with them are numerous lymphoid cells, a few polymorphonuclear leucocytes, and connective tissue cells. At these points there is also much nuclear disintegration, as is shown by numerous nuclear fragments and much granular, amorphous material. Alterations of a similar kind, but of not quite so marked a character, are found between the bases of the crypts and the muscularis. A very curious feature of the change here is the absence of mucinoblasts; in the normal intestine they are present between the crypts in enormous numbers, but a careful search has failed to reveal the presence of a single one of these cells in the tissues examined.

The muscularis mucosæ is slightly swollen, but no other change is observed. The elastic tissue network of this layer seems entirely normal.

The submucosa is slightly swollen. There is here also a remarkable decrease in the number of mucinoblasts, there being scarcely any of them remaining in the tissues. Immediately beneath the muscularis there are considerable collections of lymphoid cells and a few polymorphonuclear leucocytes in the tissues of the submucosa, these usually lying around the smaller bloodvessels. In these situations there is often considerable cellular fragmentation, the connective tissue cells seeming especially to suffer. The collagenous tissue of the submucosa has not apparently undergone any alteration, but the elastin does not universally stain in a perfectly normal manner; the external elastic lamina of the smaller arteries have suffered most. The epithelial cells lining the inner coats of the bloodvessels are swollen. Where lymph nodes are present some of their cells always exhibit fragmentation, and there are numerous large phagocytes in the lymph channels in and around them.

The circular muscular coat is markedly swollen; for the most part the individual fibres can be seen to be much further separated than they are in health, but scattered throughout this layer there are irregularly shaped collections of fibres that preserve their normal relation to each other. Especially under low powers the appearances that result from this condition in transverse sections are very striking. The elastic tissue network between the fibres is little if any altered.

The longitudinal muscular coat presents the same alterations that are shown in the circular layer, but differ in that they are never so marked.

The subserous and serous coats are normal.

EXPERIMENT III. **Duration, about six and a half days.**

Subacute changes in the large intestine resulting from the administration of colchicum.

To a dog weighing 7 kg., 4 c.c. of the fluid extract of colchicum were given by the stomach every two days until the animal had received four doses; it died during the night following the last dose. After the administration of the drug diarrhœa set in, the dog presented unmistakable evidence of being quite sick, and after each succeeding dose grew worse until death resulted. No blood was ever observed in the stools of the animal, but there was much mucus.

On post-mortem examination the large intestine was found to be contracted, very pale externally, and almost entirely empty. The mucosa showed but little change in the upper portion of the gut, but lower down was distinctly reddened; the change, as usual, was found most pronounced on the tops of the rugæ. The small intestine showed similar alterations, but the condition was by no means so marked as in the large gut.

Sections prepared for microscopic examination show no change to the unaided eye. On microscopic examination it is found that the surface epithelium has been entirely eroded away, and, in some situations, its place is occupied by a thin layer of mucus and necrotic material. The epithelium of the entire crypts shows more or less catarrhal change. This, as might be expected, is most marked in the upper two-thirds of these glands, where the changes are universally quite severe. In these situations the cells are frequently detached from their basement membranes and lie singly or in clusters in the lumina of the crypts; they are rounded, oval, or irregular in form, their protoplasm is intensely acidophilic, and quite frequently the nuclei no longer stain with basic dyes. In some instances the nuclei show marked alterations, but in others they appear smaller than normal, are surrounded by no nuclear membrane, and are intensely basophilic; this last characteristic is, when present at all, so pronounced that the nuclei appear perfectly homogeneous throughout. In some cases the cellular membrane has ruptured, and the cells are evidently in varying stages of disintegration. When stained properly these cells invariably give more or less pronounced mucin reaction, and mucin is found between them. Not infrequently there are present toward the free ends of the crypts small, oval-shaped, cystic dilatations varying very much in size, some being but little larger than the crypts and others having diameters two or three times as great. In the centres of these crypts there are collections of cells with deeply staining nuclei and intensely acidophilic protoplasm that exhibits the mucin reaction. These cells in every way resemble those already referred to as being frequently present in the undilated crypts. Between these cells more or less free mucus is invariably found. Surrounding these masses of cells there is always a distinct layer of nearly normal epithelium, but this is usually detached from the basement membrane. The cells found in these cysts in every way resemble those that occur in the crypts in the more acute changes resulting from colchicum.

In the deeper portions of the glands the epithelial cells very generally remain attached to their basement membranes, but the vast majority of them exhibit the mucin reaction. Quite a number of these cells have, however, degenerated, and, under these circumstances, they exhibit the usual change—*i. e.*, the cells are extremely irregular in form, their protoplasm is unusually acidophilic, and their nuclei stain feebly or not at all with basic dyes. Occasionally there are also seen rounded or oval cells, with intensely acidophilic protoplasm and small, deeply staining nuclei; here, as elsewhere, these cells always lie loosely in the lumina of the crypts.

In the upper portion of the crypts, where the catarrhal changes are most marked, the elastic basement membranes do not take the stain well, evidently being in a degenerate condition.

The supporting structures that lie between the crypts show but little change except at the free surface of the gut, where, as has been before stated, the desquamation of the epithelium has left them entirely exposed where not covered by mucus. The tissues are somewhat swollen as the result of the dilatation of the lymph vessels, and always show a mild degree of degenerative change. There are present here many large phagocytes, quite a number of connective tissue cells, and a few lymphoid cells. Along the free surface of the intestine the protoplasm of these cells is abnormally acidophilic, and the nuclei are often fragmented and do not stain well. The collagenous tissues of the same regions are granular and are universally acidophilic, but are much less altered than the neighboring elastic tissues. The tissues here frequently contain small bacilli that appear to belong to the colon group. The bloodvessels are contracted and contain but little blood. All through the upper portion of the mucosa there is the same remarkable absence of mucinoblasts observed in the previous case. The tissues between the bases of the crypts show no change, with the exception that the mucinoblasts have almost entirely disappeared, and the few that still remain are small, ill-formed, and do not give the mucin reaction distinctly. The fibres of the muscularis mucosæ are pushed apart by fluids that have collected in the parts, but further than this there are no changes.

The submucosa is slightly swollen, but is otherwise normal.

The circular muscular coat is somewhat swollen. The elastic network shows no change.

The longitudinal muscular coat is also somewhat swollen, but no other change is found.

The subserous and serous coats are normal.

Résumé of the Changes that are Produced in the Intestine as the Result of the Administration of Colchicum.

Acute. (Twelve hours.) The mucous surface of the intestine shows here and there dark bluish-red discolorations, occurring principally on the tops of the rugæ. The intestine otherwise appears normal.

The epithelium that lined the surface of the intestine in health is for the most part absent, and that that covered the mouths and necks of the crypts has in many instances shed off. The cells of the deeper portions of the crypts present slight catarrhal change, and all contain more or less mucin. The glands are considerably compressed toward their free ends, which is the result of the collection of fluids and cells in the intervening tissues.

The interglandular tissues contain numerous hemorrhagic areas. The pre-existing cells, as well as the red blood cells that have been poured into the parts, generally show necrotic changes. Mucinoblasts are very numerous and quite large; they are sometimes found in the lumina of the crypts.

Changes less acute than the preceding. (Fifty-six hours.) At the post-mortem the large intestine of the animal was found empty and the mucous surface of the gut was very red.

On microscopic examination the surface layer of epithelial cells was found entirely absent. The cells have likewise shed off from the mouths and necks of the crypts, and frequently lie in the openings of the glands in varying stages of disintegration. In the bodies and bases of the crypts the cells are swollen and irregular in form, and have not uncommonly desquamated; but in these situations, even when not attached to their basement membranes, they generally stain in practically a normal way. All of the epithelial cells found, even the necrotic cells at the mouths of the crypts, show within their protoplasm more than the usual quantity of mucin.

The interglandular substance is necrotic on its free surface, and the tissues are decidedly swollen somewhat lower down. In the latter situations the bloodvessels are universally enormously dilated and have in many instances ruptured, with the result that quantities of blood are found everywhere in the tissues. There are no changes in the normal cellular constituents of the parts further than that mucinoblasts are entirely absent. There are here and there small collections of polymorphonuclear leucocytes.

The submucosa is slightly swollen, and there are found in the lymph spaces here and there a few polymorphonuclear leucocytes.

Subacute. (Six and a half days.) On examination the intestine was found empty and its mucous surface generally pale, though over the lower half of the large bowel the mucosa was somewhat redder than that of the upper portion of the gut.

On microscopic examination the surface layer of epithelium is found to have entirely disappeared, and the cells that lined the mouths and necks of the crypts have likewise desquamated. The epithelial cells in the bodies and bases of the crypts are swollen and irregular in form, and in some instances have shed off from their basement membranes. Almost all of the cells contain mucin, so that this substance is evidently being formed in more than the usual quantity.

The free surface of the interglandular tissues are distinctly necrotic. At a short distance below the surface the tissues lying between the crypts are somewhat swollen as a result of the presence of increased quantities of fluids in the parts. The bloodvessels, instead of being dilated, generally appear to be somewhat contracted. Mucinoblasts are almost entirely absent.

CHAPTER VI.

EXPERIMENTS TO DETERMINE THE EFFECTS PRODUCED BY PURE CARBOLIC ACID ON THE LARGE INTESTINES OF DOGS.

EXPERIMENT I. **Duration, between twelve and twenty-four hours.**

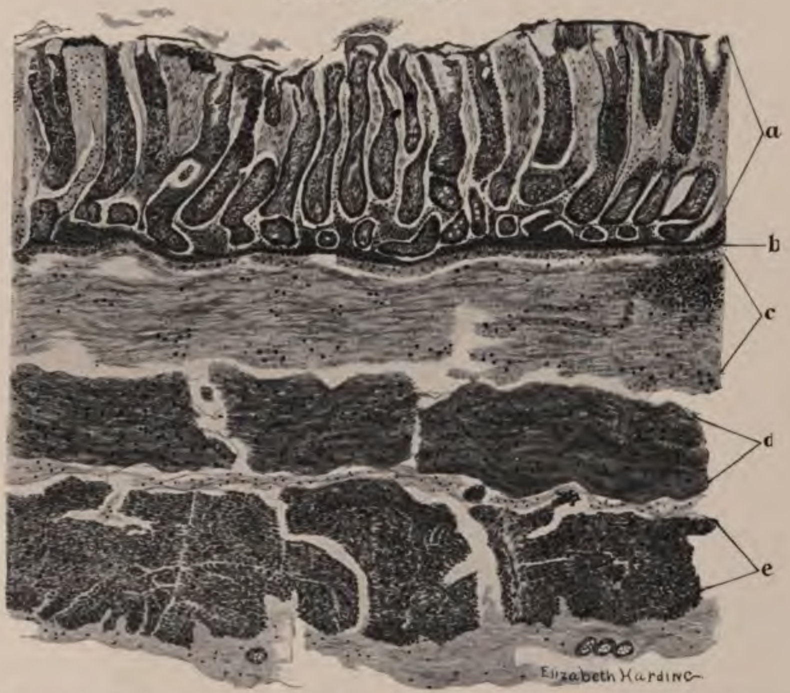
ON February 6, 1901, at 11 A.M., 10 c.c. of pure carbolic acid were injected into the large intestine of a medium-sized dog. On the following morning the animal was found dead, and an autopsy was at once made.

On examination the lower half of the intestine was found to contain a small quantity of fecal matter. The walls of the gut in this situation were thickened, and they were so stiff that it required some little force to push them together before the viscus was cut open. The mucosa was of a grayish-red color and presented the appearance of superficial ulceration. The rugæ were not numerous, nor were they very prominent; the mucosa covering them presented an appearance in every way similar to that of the neighboring portions of the gut.

On microscopic examination it was found that the epithelium that covered the surface of the intestine and the tissues that lay immediately beneath have entirely disappeared, there being in their stead a mass of granular material containing much mucus. The epithelial cells lining the mouths of the crypts have likewise in some instances disintegrated and disappeared, but the tissues intervening between these portions of the glands, though greatly degenerate, are still present in their normal situations. The cells lining the necks of the crypts are generally still attached to their basement membranes, and, without exception, their protoplasm is almost entirely made up of mucin. Those parts of the protoplasm of the cells that do not consist of mucin are finely granular and take basic stains in preference to acid ones; as the nuclei are visible in none of the cells, this in all probability is the result of the fact that they have disintegrated and the nuclear substance has been diffused into the surrounding protoplasm. The cells lining the bodies of the glands show no alteration further than that their protoplasm is made up almost entirely of mucin. The epithelial cells lying in the basal portions of the glands appear much shorter than normal, and the protoplasm toward the free ends of the cells is invariably filled with mucin. In every instance the crypts are completely filled with masses of mucus, this substance being very largely present even in the basal portion of the lumina of the crypts. In the deeper portions of the glands the protoplasm of the epithelial cells seem to have undergone a mucin transformation, and in most instances the cells have ruptured—which would account for the fact that the cells appear much shorter in the situations referred to than they are found in health. In the regions most diseased the basement membranes of the crypts no longer take their specific stains and cannot be made out with certainty.

As has already been remarked, the superficial portions of the interglandular substance projects into the lumen of the gut, the epithelial cells normally covering these structures having entirely sloughed away. Of those that are normally present the only structures that still remain in this area are the bands of collagenous tissue, between which there is present a granular débris that has resulted from the destruction of the pre-existing cells and of the red blood-corpuscles that have emigrated into the part. The tissues here, as a rule, are slightly basophilic; this appears to have been the result of the disintegration of the pre-existing cells of the part and the diffusion of the chromatin that was contained within them into the surrounding tissues. Deeper down between the necks and bodies of the glands the tissues are considerably swollen, this being due to the rupture of the blood-vessels and to the effusion of blood into the surrounding tissues. The red blood cells composing these ecchymotic areas have universally undergone degenerative change, and there remains nothing except a granular débris representing them. As a result of this the tissues stain in an almost uniform manner with acid dyes, the granular débris resulting from the disintegration of the red

PLATE XII.



Specimen from about the middle portion of the large intestine of a dog into which 10 c.c. of pure carbolic acid had been injected from twelve to twenty-four hours before the death of the animal. The tissues were fixed in Bensley's solution and stained with hæmalum, muchæmatein, and picric acid. Beck ¼ inch, Oc. 1 inch. *a.* Mucosa, showing all of the crypts filled with mucin, and the intervening substance swollen and more or less necrotic. *b.* Muscularis mucosæ, the tissues of which stain very badly. *c.* Submucosa, the tissues of which also refuse to take the stain in the usual way. *d.* Circular muscular layer. *e.* Longitudinal muscular layer. (Exp. I.)

blood cells and the collagenous tissue being colored almost exactly alike. In specimens prepared by Van Gieson's method the structures found in these situations are dyed a reddish-yellow hue, the bands of collagenous tissue being no longer colored of the intense red color which they assume under normal conditions when stained in this way. In the interstices of the tissues there are quite a number of lymphoid cells, pseudoplasma cells, and a few polymorphonuclear leucocytes, none of which stain in a perfectly normal way; the chromatin in the nuclei of these cells seems to have been diffused through their protoplasm, with the result that the entire cells show in all of their parts more or less affinity for basic dyes, and the nuclei are never brought out in a precise or clear manner. Mucinoblasts are absent not only from the interglandular substance here, but are nowhere found within the mucosa. Passing down toward the bases of the glands the changes in the tissues gradually become less marked, there is not so much blood effused into the parts, the cells stain more distinctly, and it is not uncommon to find bloodvessels the walls of which are still preserved, though they are enormously dilated and contain thrombi composed of white blood-corpuscles and disintegrating red blood cells. Of course, as a result of the swelling which has occurred between the crypts these structures are more or less compressed; but this is not so markedly the case as one might suppose, for they, as a rule, do not measure less than 60μ in diameter. Changes of a similar kind are likewise found around the basal portions of the glands, but they are not altogether so intense, there being but little blood in the tissues here, and the cells that are present stain fairly well.

The muscle fibres composing the muscularis mucosæ have in a large measure disintegrated, which doubtless explains the fact that but few rugæ were found on the surface of the intestine at the time that the post-mortem was made. In many cases the forms of the muscle fibres are in a measure preserved, but in all instances in the regions that have suffered most change they consist of a mass of acidophilic granules, and their nuclei take the basic stain but slightly or not at all. Quite as commonly the cells have entirely broken up and are represented by a mass of granular débris lying loosely in the tissues. The elastic tissue network of this layer has likewise disintegrated and no longer takes its specific stains.

The tissues composing that layer of the submucosa that is in contact with the muscularis mucosæ are in a partially degenerate condition. The elastic tissue fibrils can no longer be detected, and the collagenous tissue bands are swollen, and when stained by the method of Van Gieson are, like the tissues lying between the crypts, colored reddish-yellow instead of the bright red hue which they assume under normal conditions when treated in this way. The nuclei of the connective tissue cells in this area do not stain with their usual intensity with basic dyes. No mucinoblasts are found in the deeper layers in any of the parts of the diseased tissues. In the deeper portions of the submucosa the elastic tissue and collagenous tissue fibrils stain in a normal way, and there appears to be practically no change in the tissues. The bloodvessels in all parts of the submucosa are enormously distended and contain thrombi in which are found white blood cells and many disintegrating red blood-corpuscles; no fibrin is ever found in these vessels. The walls of the vessels in the superficial portions of the submucosa stain as do the surrounding tissues, and have evidently undergone decided degenerative change. In the deeper portions of the submucosa the walls of the vessels are intact with the exception only that the epithelial cells lining them have shed off, exposing the elastic tissue basement membranes beneath, which always stain in a normal manner.

No changes are found in the other coats of the intestine, with the exception that the walls of the bloodvessels show slight alteration; the lining epithelial cells have usually shed off from their basement membranes, and may even be found lying loosely in the lumina of the vessels.

EXPERIMENT II. **Pure carbolic acid. Duration, eighteen days.**

On February 6, 1901, 2 c.c. of pure carbolic acid were injected into the rectum of a large dog. The animal appeared to suffer no ill effects as the result of the administration of the drug. Injections of a like quantity of the acid were given on the 8th, 10th, 12th, 14th, 16th, 18th, 20th, and 22d of February. The dog grew somewhat thinner during the course of the treatment, and after the acid had been given several times he suffered with diarrhœa; the stools contained much mucus mixed with blood. On February 24, 1901, the animal was killed with chloroform, and an autopsy was at once made. The large intestine was found to be practically empty, the mucous surface of the lower half of the gut was of a reddish-gray color, with here and there areas that were intensely blood-stained. The mucosa presented the appearance of superficial ulceration. The rugæ were not particularly numerous in the area showing the greatest amount of alteration, but somewhat higher up these elevations were very prominent both as regards number and size; the mucous membrane covering their apices did not appear more greatly affected than that of the surrounding portions of the intestine. The gut was decidedly swollen in the affected regions.

On microscopic examination varying degrees of alteration in the mucosa were found, evidently depending upon whether the parts had been with greater or less frequency subjected to the action of the acid. In some areas the only changes observed are a desquamation of the epithelial cells that normally covered the surface of the intestine and slight catarrhal changes of the epithelial lining of the mouths and necks of the crypts. Under such circumstances there are generally found very large plugs of mucin in the mouths of the crypts that in every way resemble those found in the more acute process, except only that they are not, as a rule, so large. The cells lying in the deeper portions of the glands show no alterations further than that they generally contain more mucin than is usual in health. These masses of mucin seem to have plugged up the openings of the crypts in some instances, and the collection of secretion beneath has caused a mild degree of dilatation of the bodies and bases of the glands; the contents of the resulting cysts consist of a small amount of mucin, intermingled with which there is much granular débris. The cells lining these cystic dilatations of the glands show but little alteration, the only change observed is that they have the appearance of being somewhat swollen. While the deeper portions of the crypts are, as a rule, not affected, some of them present striking catarrhal changes, this having gone on to such an extent in a few instances that the glands have been entirely stripped of their epithelium. It is of interest to note that the protoplasm of the epithelial cells in and around the diseased areas contain a great many minute granules that take the basic stain; these granules are often present in such numbers that the cells appear of an almost uniform dark color after staining in toluidin-blue and eosin. The basement membranes lying beneath the catarrhal epithelium, as a rule, fail to take their specific stains, but around the basal portions of the glands there is no obvious alteration in these structures.

The interglandular substance in these situations is decidedly swollen as a result of the presence of quantities of fluids in the parts. Generally there is a notable absence of the cellular constituents that are usually found in these situations, the cells appearing to have been carried away by the lymph currents. This change, as a rule, is only confined to the supporting structures lying between the mouths and necks of the crypts, but in some instances almost all of the cells that originally lay between the glands have disappeared. Of the cells that still remain in the parts a very large percentage consists of mucinoblasts, which have evidently increased considerably in the affected region. The collagenous and elastic tissue fibrils show no change.

The tissues lying deeper down beneath the lesions that have just been described show no alterations.

In some situations the changes are of a more pronounced character. Here there has been quite a degree of ulceration of the mucosa, the process extending to a variable depth into the tissues. The surfaces of these ulcerated areas are composed of a granular débris resulting from the destruction of the pre-existing tissues of the parts, and along with this there are quite a number of polymorphonuclear leucocytes and a few lymphoid cells. There is no clear line of demarcation between the partially necrotic tissues of the surface and the normal ones that lie at a lower level, as they merge insensibly into each other. The epithelial cells that line the remnants of the glands show no very pronounced alteration further than that their protoplasm is somewhat more basophilic than is usual; exceptionally, they exhibit catarrhal changes, and in some instances have entirely shed off from their basement membranes. The intervening supporting tissues are swollen as a result of the accumulation of fluids and the dilatation of the bloodvessels, and of the accumulation in the parts of polymorphonuclear leucocytes, lymphoid cells, plasma cells, and quite a number of the large phagocytes of Metschnikoff.

The tissues lying beneath these lesions show alterations depending upon the depth to which the ulceration extends; when the changes are superficial the alterations, as a rule, do not extend below the mucosa; but in instances where they pass downward more deeply the muscularis mucosæ is in some cases swollen, and there are sometimes found between the muscle fibres small collections of polymorphonuclear leucocytes; where the necrotic processes are quite extensive the upper layer of the submucosa may show alterations of a similar kind.

In some cases the entire mucosa has been destroyed, though the actual ulceration was never observed to extend below the muscularis mucosæ. The floors of such ulcers are composed of a granular débris, intermingled with which there are many polymorphonuclear leucocytes and lymphoid cells. In the neighboring partially normal tissues there are numerous polymorphonuclear leucocytes, a great many gigantic mucinoblasts, multitudes of large phagocytes of Metschnikoff, and a few lymphoid and plasma cells; the connective tissue cells that originally lay in the parts have for the most part disappeared. These changes extend downward through the muscularis mucosæ into the outer layers of the submucosa, but, becoming gradually less marked, finally cease altogether in the vicinity of the circular muscular coat. Fibrin is never found in the diseased areas, nor does there appear to have been an increase in the collagenous tissues. On the surfaces of the ulcers both the collagenous and elastic tissue fibrils fail to take the stain in a normal way, but lower down they present no alteration. It is noteworthy that the newly-formed epithelium has partially grown over the surfaces of the ulcerated areas in many instances; these recently formed epithelial cells are large and quite tall near the points where they come in contact with the epithelium of the surrounding normal tissues, but as they grow away over the diseased surface they become smaller and smaller, and finally terminate in minute, flattened cells at a greater or less distance from the edges of the ulcers. These cells often contain mucin, and mitoses are sometimes observed within them.

From the preceding description it will be seen that there result in the tissues, from the repeated application of carbolic acid, changes closely simulating those that are found in the bowel in the subacute forms of amœbic dysentery.

No changes are observed in the other coats of the intestine.

Résumé of the Changes Produced by Carbolic Acid.

Acute. (Twenty-four hours.) At the necropsy the gut was found to be decidedly thickened and much stiffer than usual. The mucosa presented the appearance of superficial ulceration.

On microscopic examination it is found that the superficial epithelium and that lining the mouths of the crypts has entirely disappeared. The epithelial cells lying in the lower portions of the glands still line their basement membranes in the normal way; but they have within them, without exception, great masses of mucin. The lumina of the crypts are in all instances likewise completely filled with this substance.

The interglandular tissues contain great quantities of blood, the cells of which have entirely disintegrated. The granular débris that results from the breaking up of the red blood cells is present in such quantities that none of the pre-existing tissues of the parts can be made out.

The muscle fibres of the elastic tissues constituting the muscularis mucosæ show pronounced degenerative change.

The connective tissues of the submucosa do not stain well, and they are evidently in a more or less degenerate state. The blood-vessels in this coat are greatly dilated and are not uncommonly thrombosed. The walls of these vessels likewise show degenerative change. No mucinoblasts are found in any part of the intestinal wall.

Chronic. (Eighteen days.) On post-mortem examination the walls of the lower portions of the large intestine were found decidedly swollen, and the mucosa was somewhat redder than usual.

Microscopic examination shows that the changes in the intestine vary very much in different situations. In some cases there are only slight catarrhal alterations, but it is noteworthy that there is a greatly increased amount of mucin being formed in all instances. The epithelial cells, even where otherwise normal, appear unusually basophilic. The basement membranes upon which these cells lie do not stain well.

The interglandular tissues here are decidedly swollen as the result of the presence of fluids. The tissues contain an unusual number of mucinoblasts.

In some cases there is actual ulceration of the mucosa, which extends to a much greater depth in some situations than in others. In these areas the epithelial cells lining the remnants of the crypts show comparatively little change, but the intervening tissues are generally swollen and contain, in addition to fluids, many polymorphonuclear leucocytes, lymphoid cells, plasma cells, and large phagocytes of Metschnikoff. The bloodvessels here are decidedly dilated.

In some instances the ulceration extends down into the muscularis mucosæ, the fibres of which are decidedly granular and are frequently pushed apart by collections of polymorphonuclear leucocytes. Where the ulcers are old newly-formed epithelium has grown out over them from the surrounding epithelial surface in many instances.

CHAPTER VII.

EXPERIMENTS TO DETERMINE THE EFFECTS OF SOLUTIONS OF COPPER SULPHATE ON THE LARGE INTESTINES OF DOGS.

EXPERIMENT I. **Duration, forty-eight hours.**

To a dog weighing 8 kg., 4 gm. of copper sulphate dissolved in 50 c.c. of water were given by the mouth. The dog had been previously anæsthetized, so that the drug was not vomited. Twenty-four hours later the animal frequently vomited, and was evidently quite sick. On the following day—forty-eight hours after the first dose was given—4 gm. of copper sulphate were again administered in 50 c.c. of water. Notwithstanding that a part of this was vomited, the animal shortly after passed into a state of collapse and died in an hour from the time the chemical was given.

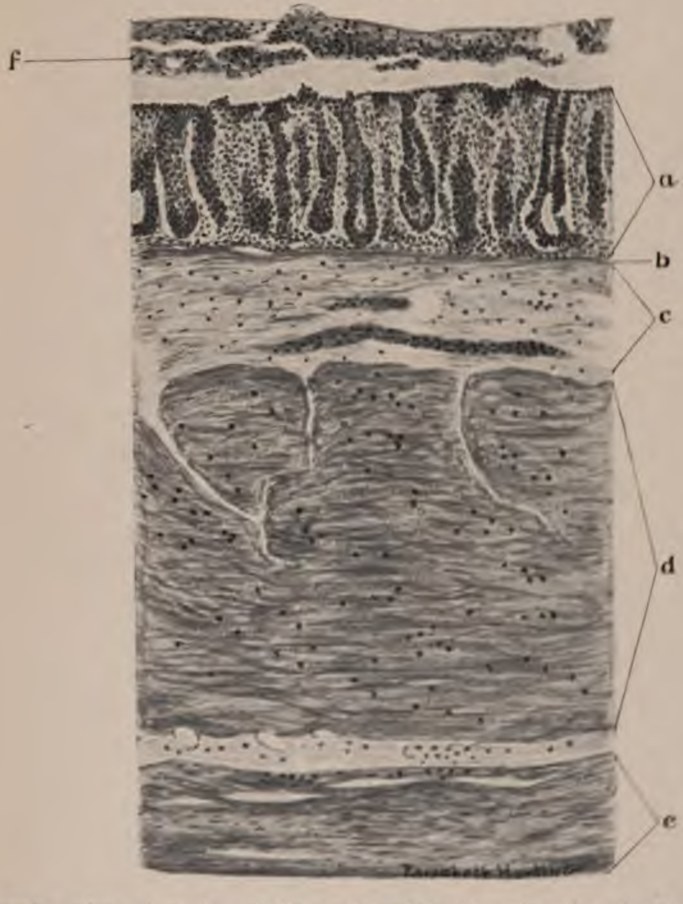
A post-mortem was at once made. The large intestine was found practically empty. Its mucosa was moderately reddened, the tops of the rugæ showing, as usual, the greatest degree of change. The small intestine exhibited a similar alteration, but to a much less degree.

Microscopic sections when viewed with the unaided eye show no alteration.

On microscopic examination the superficial epithelial layer is found very generally absent, and, taking its place, there is an almost uniform, very thin layer composed largely of mucus, intermingled with which there are numerous bacteria and some granular débris. Further than that there are a greater number of mucin-bearing cells than normal, the epithelial cells of the crypts show no change except immediately at their mouths, where, occasionally, a few of the cells have desquamated. There are about the usual number of mitotic figures in the basal cells.

The elastic tissue basement membrane is not greatly changed,

PLATE XIII.



Specimen from about the middle portion of the large intestine of a dog that had received by the mouth a solution of copper sulphate forty-eight hours, twenty-four hours, and again one hour before death occurred. The tissues were fixed in Bensley's solution and stained with hæmalum, muchæmatein, and picric acid. Beck [illegible] inch, Oc. 1 inch. *a.* Mucosa, upon the surface of which there is a mass of mucin containing a granular débris (*f*), and between the crypts there are found multitudes of free red cells, many large phagocytes and a few polymorphonuclear leucocytes. *b.* Muscularis mucosæ. *c.* Submucosa. *d.* Circular muscular layer. *e.* Longitudinal muscular layer. (Exp. I.)

but takes the stain badly or not at all from the middle of the crypts outward to their ends.

The tissue that intervenes between the crypts is about as often normal as otherwise, but in some situations, especially at the apices of the rugæ, shows marked alteration; while there appears no plausible explanation for this peculiarity of the lesions produced by copper sulphate, the change is so pronounced and of such a peculiar kind that it appears to be entirely characteristic. In the affected regions the crypts are widely separated by disintegrated blood, and, in addition to the blood cells, there are found many lymphoid cells, quite a number of pseudoplasma cells, and a comparatively large number of phagocytes. The phagocytes contain in some instances nucleated cells, but always many necrotic red cells. The collagenous tissue, even in the areas most affected, is practically normal; however, in some instances it takes the stain poorly. No bloodvessels can be made out in the diseased region. The changes are limited almost entirely to the outer half of the mucosa, but sometimes extend even to the muscularis mucosæ.

In the otherwise healthy regions the bloodvessels sometimes rupture, and there of course results a localized area of hemorrhage around the affected vessel. In instances where this change has existed for quite a time the cells found in and around the diseased area exhibit similar alterations to those observed in the more pronounced lesions just described. At no point in the mucosa are there dilated bloodvessels; indeed, the vessels, if their calibre be at all changed, seem smaller and less conspicuous than normal.

The mucinoblasts have entirely disappeared from the deeper portions of the mucosa, but a few are still present in the superficial regions; these cells are, however, smaller than normal, and at most contain only a few small mucin granules clinging to their nuclei.

The muscularis mucosæ is entirely normal.

The submucosa is normal, with the exception that the mucinoblasts are diminished in number and are smaller than the cells of a like kind found in the normal intestine.

The muscular coats are normal.

The subserous and serous coats show no change.

EXPERIMENT II. **Duration, about seventy-five hours.**

On May 27, 1900, at 9 P.M., 4 gm. of copper sulphate dissolved in 50 c.c. of water were injected into the rectum of a dog weighing 6.5 kg.; before the drug was given the animal was thoroughly narcotized. On removing the rectal tube a small quantity of the copper sulphate solution ran out.

On the following morning the dog could not be induced to get up, and exhibited every evidence of being very sick. On May 30th, at 8 P.M., the injection was repeated. The animal died during the night. The post-mortem was made early the following morning.

The large intestine contained a considerable quantity of a dark brick-red grumous substance that appeared to consist largely of disintegrated blood. The surface of the intestine is of precisely the same color as the material contained within it. On close inspection the more elevated portions are found to be somewhat darker in color than the intervening depressions.

On microscopic examination of sections of the diseased intestine the mucosa is found to be entirely destroyed, but here and there are necrotic masses which, from their situation, are evidently remains of the structures contained in this layer.

The muscularis mucosæ has also, in most instances, entirely sloughed away, and even where fragments of it remain the tissues are in a state of advanced disintegration; it is noteworthy that the elastic tissue network of this coat is still demonstrable by the method of Weigert. These various necrotic structures take the place of the mucosa and form a sort of lining for the intestine. The submucosa is greatly swollen, partly as the result of accumulations of liquids in the lymph spaces and, to an even greater extent, of an enormous collection of cells in the same situations. These cells are present in greater number in the outer layers of the submucosa, just beneath the sloughing tissues of the outer coats. In these situations many bacteria are present, and, it may be added, that they are also numerous in the deeper portions of the necrotic tissues. These bacteria are present in such numbers that it seems highly probable that they are responsible for a part, at least, of the changes that are present. The cellular masses that make up the great bulk of the tissues in the outer layer of the submucosa are made up of a great number of lymphoid cells, many red cells, and a few transitional and polymorphonuclear leucocytes; the leucocytes are apparently not present in greater number than would be warranted by the hemorrhage that has evidently occurred in the parts, and the process cannot therefore be regarded as being in any sense a suppurative one. In this part of the submucosa the fibrils of collagenous tissue, further than being widely separated from each other, show no change; but the elastic tissue stains badly in many situations, and appears to have suffered more than the neighboring fibrous structures. The bloodvessels are here always thrombosed and contain masses of disintegrating blood. The walls of the vessels show marked alterations; in most all instances the epithelial cells have desquamated, the internal and external lumina stain feebly, and the muscle fibres are swollen and granular, and their nuclei take basic dyes badly.

Passing deeper into the submucosa these cells rapidly decrease in number, the collagenous fibres are not as widely separated from each other, the elastic tissue stains somewhat better, and such marked changes on the walls of the bloodvessels are no longer observed. However, the bloodvessels are not entirely normal, for they are dilated with blood, and degenerative changes in their walls may be still seen here and there; those changes are evidently in many instances sufficiently great to permit rupture of the vessel, since the lymph spaces contain considerable quantities of blood in many localities. These localized areas of rhexis in every way—barring situation—resemble those that have been described as occurring in the mucosa in the milder degenerative process produced by copper sulphate. The submucosa mucinoblasts have entirely disappeared.

The muscular fibres of the circular coat are almost universally considerably separated from each other by accumulations between them of albuminous fluids and a few lymphoid cells. The fibres themselves in some instances appear faintly granular, but for the most part show no alteration. The elastic tissue network of the layer stains poorly, but the collagenous tissues appear to be normal. The bloodvessels show no change.

The longitudinal muscular coat shows a similar swelling between the fibres, but not to such a degree as was found in the circular layer, and the elastic tissue stains poorly. No further alteration is present.

The bloodvessels of the subserous coat are generally dilated and filled with blood, but their walls show no change further than that the elastic layers stain badly.

The elastic basement membranes of the serous coat stain poorly, but there is no other change observed in this layer.

Not a single mucinoblast was found in any part of the intestinal walls that were examined.

Résumé of the Changes Resulting from the Administration of Copper Sulphate.

Acute changes following the administration of the drug by the mouth. (**Forty-eight hours.**) On post-mortem examination the large intestine of the dog was found empty, and its mucous surface was moderately reddened.

Microscopic examination showed that the surface epithelial cells have entirely shed off, and that the cells lining the mouths of the crypts have likewise desquamated. The cells covering the necks, bodies, and bases of the crypts show no further alteration than that mucin is present in unusual quantities within their protoplasm.

The crypts, as a rule, are compressed and widely separated from each other as a result of the accumulation in the interglandular tissues of great quantities of blood, intermingled with which there are the usual cells found in the parts and many large phagocytes ; a few polymorphonuclear leucocytes are also found. There are still a few mucinoblasts present in this area ; they are small and contain only a few mucin granules. These changes are almost entirely confined to the outer half of the mucosa. It is a rather curious fact that in the deeper portions of this coat no mucinoblasts are found.

Acute changes following rectal injection of solution of copper sulphate. (**Seventy-five hours.**) On post-mortem examination the large gut was found to contain a considerable quantity of dark brick-red, grumous material resembling disintegrated blood. The surface of the intestine is practically of the same color as the peculiar substance just referred to.

The mucosa is almost entirely destroyed, there being only here and there small masses of necrotic tissue in which it is possible to recognize some of the structures that go to make up the surface layer of the intestine. In most instances the muscularis mucosæ is also destroyed.

The submucosa, especially that part of it just below the muscularis mucosæ, is greatly swollen as a result of the accumulation of fluids in the parts and of an enormous amount of hemorrhage; there are quite a number of lymphoid cells scattered through the tissues as well as a few polymorphonuclear leucocytes. The bloodvessels are, without exception, thrombosed within this area, and contain masses of disintegrated blood. The epithelial cells that line the bloodvessels have generally shed off from their basement membranes, and the walls in addition to this have evidently suffered considerably, as they present decided evidences of necrotic change. Alterations similar to these are found in every part of the submucosa, but in the deeper portions they are by no means so marked.

The muscle fibres of both the muscular coats are more or less separated from each other by the accumulation of fluids, and there are here and there found a few lymphoid cells. The muscle fibres themselves present practically no alteration.

The subserous and serous coats show no marked changes.

It is a remarkable fact that mucinoblasts are entirely absent from all parts of the intestinal wall, not a single one having been found in any of the numerous sections examined.

CHAPTER VIII.

EXPERIMENTS TO DETERMINE THE EFFECTS OF REPEATED DOSES OF CALOMEL GIVEN BY THE MOUTH ON THE LARGE INTESTINES OF DOGS.

EXPERIMENT I. **Duration, about four and a half days.**

ON November 13, 1900, a dog weighing 7 kg. was given 0.5 gm. of mercurous chloride by the stomach, and on the following day the dose was repeated. The animal suffered with diarrhœa, and was evidently very sick for two days following. On November 17th a like amount of the drug was again administered. The dog was found dead on the following morning.

At the necropsy the entire intestinal tract was found to contain a soft, grumous material that seemed to be disorganized blood. On examination the mucosa of the large intestine showed but little alteration, there being only here and there minute reddened areas over its surface that are usually, as in almost all of these experimental inflammations, most marked on the tops of the rugæ. The lower part of the large intestine has suffered somewhat more than the upper portion. The edges of the ileocæcal valve are decidedly reddened, this, however, being most marked on the upper side. The mucosa of the small intestine is decidedly reddened.

On microscopic examination the surface of the large intestine is found almost entirely free from mucus, but in some situations small masses of granular débris mixed with mucin are present. The surface epithelium has universally desquamated, and the epithelial cells lining the mouths and necks of the crypts have also separated from their basement membranes.

Quite often the cells in the mouths of the crypts, after having been loosened from their basement membranes, have been discharged into the intestinal tract and carried away, but in the majority of instances they still remain in the lumina of the crypts, clumped together in small, irregularly shaped masses. The cells in the necks of the crypts are, as a rule, still attached to their basement membranes, but in a certain proportion of cases they lie loosely in the lumina of the glands, and in some instances form clumps such as have been described as occurring in the mouths of the crypts. These loose cells are swollen, granular, and quite irregular in form; but their nuclei always stain practically in a normal manner, and their protoplasm, instead of exhibiting the usual acidophilic affinities of degenerating cells, often shows a decided tendency to take the basic stain in a more marked manner than in health. Within the protoplasm of these cells a faint mucin reaction is sometimes obtained, but in an overwhelming majority of instances this substance is not found within them; this condition is very unusual, as in almost all of the so-called catarrhal inflammations the amount of mucin is greatly increased, but in this instance the quantity is actually much less than in health. Those cells that still remain attached to the basement membranes in the necks of the crypts are unusually swollen, and their free ends often appear ragged, showing beyond doubt that necrotic changes have already begun within them; these cells, however, stain in about the usual way, and, like those that have desquamated, show much less than the normal amount of mucin within their protoplasm. The lumina of the crypts toward their free ends are usually decreased in size on account of the swelling in the intervening connective tissue. The cells that line the lower portions and bases of the crypts show practically no alteration. The only observable change is a disposition to desquamate to a limited extent, and the amount of mucin that is present within them is certainly somewhat less than is usually seen in the normal cells. This diminished mucin formation is likewise evidenced by the fact that very small quantities only of this substance, and in many instances none at all, are found within the lumina of the glands. The lymph node crypts show practically no alteration.

The basement membranes show no change.

The free surface of the tissues intervening between the crypts is covered by finely granular material in which there are many bacteria; these masses of granular débris evidently represent the necrotic cells and tissues that originally formed the outermost structures in the diseased regions. This granular material stains with acid dyes, as a rule, but there are many particles that take the basic stain with more or less intensity. In many situations there are also found considerable masses of blood mixed with this granular detritus; the red blood cells in these masses of blood are usually swollen, irregular in form, and in many instances have partially disintegrated. Polymorphonuclear leucocytes in varying stages of disintegration always occur mixed with the red blood cells, and frequently lie embedded in the masses of granular débris in situations where there is no blood. Here and there these necrotic changes in the tissues extend downward quite deeply, involving in some instances as much as the outer half of the mucosa. Under these circumstances all of the tissues in the affected area are practically destroyed, the crypts are no longer recognizable, and the intervening connective structures have lost all resemblance to the tissues normally found in these situations. The changes that are present lower down in every way resemble those that have been described as occurring where the necrotic process only involves the surface of the mucosa. Lower down the tissues are greatly swollen and frequently contain ecchymotic areas. The fibrils of both the elastic and collagenous tissue appear to be swollen, and their outlines are ill-defined; they do not react to their specific stains in the normal way. Lying between the fibrils of connective tissue there are numerous cells. These consist, for the most part, of lymphoid cells and large, finely developed plasma cells, but intermingled with them there are a few connective tissue cells and a very small number of mucinoblasts. In certain situations the tissues contain great numbers of polymorphonuclear leucocytes, and where they are present they so largely predominate that they constitute by far the greatest number of cells in the affected area, though there are always found a few lymphoid and plasma cells intermingled with them. In these situations there are many widely dilated bloodvessels, filled with blood, and the tissues are even much more swollen than in the other parts of the mucosa. In some instances this process has gone on to such a degree that the crypts have been almost squeezed out of existence as a result, and appear merely as columns of cells between the swollen connective tissues. Although carefully examined for, no bacteria were found in these situations. In those parts of the mucosa where the leucocytic infiltration is not so marked the bloodvessels are not infrequently considerably dilated, but they never show this change to such an extent as is seen where the polymorphonuclear white blood cells predominate. Here the change becomes gradually less marked as the bases of the crypts are approached, and in many instances no alteration at all is found in the deepest portion of the mucosa. It is noteworthy, however, that in addition to a slight degree of swelling of the tissue, which may or may not be present, there is a decided diminution in the number of mucinoblasts, and there are generally present quite a number of lymphoid and plasma cells. Where the leucocytes predominate the deeper interstitial structures of the mucosa are always considerably altered; the tissues are swollen, are often quite granular, and the bloodvessels are usually distinctly dilated and are filled with blood. This change does not, however, extend beneath the muscularis mucosæ.

The muscularis mucosæ shows but little alteration, the only apparent change being that there are present between the fibrils quite a number of plasma cells and some lymphoid cells. The muscular tissue and the elastic tissue network of this coat show no alteration.

The submucosa is but little affected, the most marked changes being an unusual degree of dilatation of the veins and presence of quite a number of plasma cells, and lymphoid cells just beneath the muscularis mucosæ. The endothelial cells lining some of the smaller arteries are swollen, and in some instances have desquamated from their basement membranes. In some of the lymphatics there are small collections of fibrin. This coat is somewhat swollen.

No changes are present in the muscular or serous coats.

EXPERIMENT II. **Duration, twenty days.**

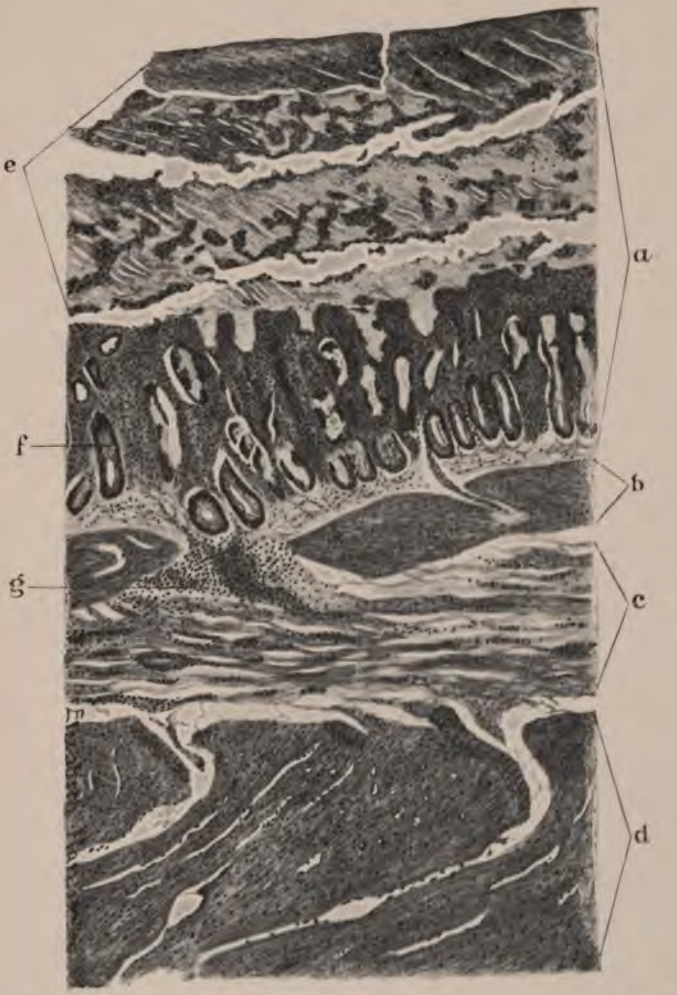
On October 18, 1900, 1 gm. of calomel was given to a dog weighing 11 kg.; the drug was mixed with the animal's food, and on the first occasion the entire dose was taken. After this a like amount of calomel was each day mixed with his food, but in most instances only a small quantity of this was actually ingested, as he evidently detected the presence of the chemical and ate very sparingly. After taking the food containing the calomel vomiting usually occurred, but notwithstanding this, at the end of a week the animal was in good spirits and showed no ill effects from the treatment further than that the discharges from the bowels were blood-stained and contained considerable quantities of mucus. A few days later the dog appeared somewhat emaciated, and after this scarcely ate any food at all. During the last week of the animal's life only a very small amount of the calomel was taken. During this period the dog daily grew thinner, became very weak, and showed every evidence of illness. He died during the night of November 7th, twenty days after the initial dose of the drug was given.

On post-mortem examination the stomach and small intestine were found entirely normal, but the lower bowel was empty and its mucous surface showed considerable alteration. The lower margin of the ileocæcal valve was of an almost black color and appeared to be superficially ulcerated. The remaining part of the large intestine was free from actual ulceration, but the mucosa was greatly reddened. This redness is greatest on the tops of the rugæ. The mucosa of the appendix was also swollen and quite red.

On microscopic examination extensive alterations are found in the mucosa of the intestines; these changes affect all parts of the intestine nearly alike, the region around the ileocæcal valve showing but little more change than the tissues in other parts of the bowel. The epithelial cells of the surface of the intestine and of the crypts have in a large measure desquamated, and secondary changes of a pronounced kind are present in the interstitial tissues lying between the glands.

Lying on the free surface of the mucosa there are very generally present masses of mucus, intermingled with which is a granular débris consisting of disintegrating cells and multitudes of bacteria. The necrotic cells that lie in these masses are evidently largely composed of the eroded surface epithelium of the gut, since

PLATE XIV.



Specimen was taken from the upper portion of the large intestine of a dog that had received daily small doses of calomel by the mouth for twenty days before death occurred. The tissues were fixed in Bensley's solution and stained by the method of Van Gieson. Beck ⅙ inch, Oc. 1 inch. *a.* Mucosa, the surface of which is necrotic (*e*), and in the deeper portions the epithelial cells of the crypts exhibit catarrhal changes (*f*), and in the intervening tissues new formation of fibrous tissue is going on, and there are present many lymphoid and plasma cells. *b.* Muscularis mucosæ, which is interrupted at (*g*) by the edge of a lymph node. *c.* Submucosa. *d.* Circular muscular layer. The longitudinal muscular layer is not included in the drawing. (Exp. II.)

this layer of cells is universally absent. Necrosis of the upper portions of the crypts and of the intervening tissues is present in some situations. The mouths and necks of Lieberkuehn's crypts show at all points marked catarrhal alteration ; the epithelial cells have almost entirely shed off from their basement membranes, are exceedingly irregular in form, in many instances swollen, and their nuclei no longer react to basic dyes ; these desquamated cells lie together in masses in the lumina of the crypts from which they come, and in not an inconsiderable proportion of instances have entirely broken up, and there remains only a granular débris representing them. Mucin is present in considerable quantities both within the epithelial cells in these situations and lying loosely in the lumina of the crypts. Lower down in the bodies of the glands the epithelial cells show less extensive change, though at no point do they appear entirely normal. Even here they have in some instances desquamated, and very generally show traces of mucin within their protoplasm. Even those cells that have not shed off from their basement membranes are more or less granular, and are frequently swollen to such an extent that the lumina of the crypts in which they lie are in a large degree obliterated. Mitotic figures are numerous in all parts of the crypts, but are especially common toward the bases of these glands.

The basement membranes of the crypts are practically unaltered.

The tissues intervening between the crypts are greatly increased in amount, and show along the free surface of the mucosa most pronounced necrotic change ; in some instances, as has been before remarked, these structures have been eroded away for a considerable distance down into the mucosa. The free surface of these tissues is very ragged and irregular, and consists of greatly swollen masses of collagenous tissue that in its outermost portion is exceedingly granular and stains deeply with acid dyes ; lying within these tissues there are a few connective tissue and lymphoid cells, but, on the whole, they contain less than the usual number of cellular elements. The elastic tissue fibres in these situations fail to take the stain, but do not seem to be in a greater degree diseased than the neighboring fibrous structures. A little deeper down the tissues no longer exhibit necrotic changes, but contain multitudes of most exquisite plasma cells, a great many lymphoid cells, and about the usual number of mucinoblasts. The fibrous structures have greatly increased in these areas, with the effect of diminishing the size of the lumina of the enclosed crypts. The bloodvessels in this region are in many instances considerably dilated, but there is no appearance of leucocytic infiltration into the tissues, nor were hemorrhages in any instance observed. Passing downward into the deeper portion of the mucosa the changes become less and less pronounced, so that around the bases of the crypts there is only here and there an increase in the fibrous tissue structures; however, there are universally present large quantities of lymphoid cells and numerous plasma cells. Mucinoblasts are found in these situations in about the usual numbers.

The muscular and elastic tissues of the muscularis mucosæ show no change, but there are found between the fibrils numerous lymphoid cells and not an inconsiderable number of plasma cells.

The submucosa shows no alteration, with the exception that it contains more lymphoid cells than is usual in health, and there are here and there circumscribed collections of plasma cells.

The muscular, subserous, and serous coats show no alteration.

Résumé of the Changes Occurring as a Result of Poisoning by Calomel.

Acute. (Four and a half days.) The intestine shows no change further than that there are found scattered over the mucosa minute areas that are somewhat redder than the surrounding surfaces.

The epithelial cells that covered the surface of the bowel, and the mouths and necks of the crypts have universally desquamated. Many of the shed-off cells still remain in the lumina of the crypts, and are swollen, very irregular in form, and contain much less mucin than is usually seen in the cells found in these situations. In some instances there are very small areas in which the outer portions of the glands and the intervening connective tissues have undergone complete necrotic change. Around the edges of these areas, and just beneath the surface of the intestine generally, there are many dilated bloodvessels filled with blood, and around these there are considerable collections of polymorphonuclear leucocytes. Hemorrhages into the tissues are not uncommon. In addition to the polymorphonuclear leucocytes there are the usual numbers of lymphoid cells, pseudoplasma cells, and a few mucinoblasts. In many instances the interglandular substance is so swollen that the crypts are very much compressed. These changes extend downward through the mucosa, but become less and less until at the edges of the muscularis mucosæ there are practically no alterations.

The deeper coats show no change.

Chronic. (**Twenty days.**) On examination the large intestine was found to be very much inflamed. The mucous surface in the vicinity of the ileocæcal valve was almost of a black color, this being evidently due to the formation of the sulphide of mercury. The tissues in this situation have the appearance of superficial ulceration, but this is found in no other part of the intestine. The mucosa of the intestine is almost uniformly reddened. The mucosa of the appendix shows a similar change.

The epithelial cells that covered the surface of the intestine, and the mouths and necks of the crypts, have universally desquamated, and those that line the deeper portions of the glands are swollen and irregular in form, and in some instances have also shed off.

The surface of the interglandular tissue is necrotic. Lower down the tissues are swollen and contain many lymphoid and plasma cells. There has been much new formation of fibrous tissue. These alterations extend no deeper than the mucosa.

CHAPTER IX.

EXPERIMENTS TO DETERMINE THE EFFECTS PRODUCED ON THE LARGE INTESTINES OF DOGS AS A RESULT OF THE INJECTION OF TINCTURE OF IODINE.

EXPERIMENT I. **Duration, twenty-four hours.**

ON January 15, 1901, 10 c.c. of tincture of iodine (U. S. P.) were injected into the large intestine of a dog. Twenty-four hours later the animal was killed with chloroform, and an autopsy was at once made. The lower half of the large intestine contained no fecal matter, and the mucosa in this portion of the gut was decidedly reddened. The transverse rugæ were quite numerous, but the mucous membrane covering these elevations was no redder than that upon the surrounding surfaces.

On microscopic examination the surface layer of epithelial cells that normally covered the mucosa is found entirely absent, and the tissues that immediately underlay these cells, as well as some of the epithelial cells that covered the edges of the mouths of the crypts, have likewise become necrotic and sloughed away. It is, however, noteworthy that catarrhal changes are nowhere observable in any of the cells that still lie in their normal positions in any of the parts of Lieberkuehn's crypts, this being true even of the cells at the margins of the lesions just referred to. Notwithstanding that catarrhal changes are nowhere found, it is of considerable interest to note that mucin is entirely absent from the cells of the crypts that lie in the regions most affected, nor is that substance ever present in the lumina of the crypts. The basement membranes upon which the epithelial cells lie are entirely normal.

The most pronounced changes found in the intestine are those that occur in the interglandular substance of the mucosa. In these areas the bloodvessels are enormously dilated and are filled with blood; in many instances they have ruptured, and when this has occurred quantities of blood are found effused into the neighboring tissues. In addition to the free red blood cells there are a considerable number of lymphoid cells, a great many plasma cells, a few mucinoblasts, and polymorphonuclear leucocytes. It is of some interest to note that those mucinoblasts that still remain in the parts are small and even more irregular in shape than usual, and in the liquids immediately surrounding them there is a zone in which the mucin reaction is distinctly obtained; it would thus appear that the mucin was undergoing solution at the time the animal was killed. It should, perhaps, be stated that the stain with which the above reaction was obtained was carbol toluidin-blue and not Unna's alkaline methylene-blue, which, on account of the fact that it dissolves out the mucin, frequently gives the appearances around mucinoblasts that have just been described. In addition to the cellular elements that are so numerously present in the interspaces of the tissues there are many small cellular fragments and a considerable quantity of fluids. The pre-existing collagenous and elastic tissues normally found in the parts present no perceptible alterations. It is, of course, obvious that much distention of the interglandular substances must have resulted from the various pathologic alterations that have been described, and as a result the crypts of Lieberkuehn have been compressed to such an extent that oftentimes they are scarcely more than one-half of their normal diameter. The changes above recorded are, as a rule, much more pronounced in the outer half of the mucosa, but always extend to a greater or less extent down to the muscularis mucosæ.

The only changes observable in the muscularis mucosæ are that there are here and there small collections of lymphoid cells, intermingled with which there are commonly a few polymorphonuclear leucocytes.

The layer of the submucosa lying next to the muscularis mucosæ also shows here and there small collections of lymphoid cells, and a few polymorphonuclear leucocytes are in addition occasionally found. The bloodvessels in this situation are also rather unusually prominent, seem somewhat dilated, and are always filled with blood. No further changes are found in this coat.

The other coats of the intestine are normal.

EXPERIMENT II. **Duration, eighteen days.**

On January 15, 1901, 10 c.c. of tincture of iodine (U. S. P.) were injected into the rectum of a medium-sized dog. On the following day the animal appeared weak and was observed to pass considerable quantities of bloody mucus. The injections were repeated on the 18th, 21st, 24th, 27th, and 30th of January, but for the reason that the animal was so decidedly affected by the first dose, only 5 c.c. of the iodine solution were afterwards given. During the period when the dog was receiving these injections he became rapidly emaciated and suffered continually with diarrhœa. On the morning of February 2, 1901, eighteen days after the first injection was given, the animal was found in a dying condition; chloroform was administered until death was produced, and an autopsy was at once made. The large bowel was almost empty, but there were present here and there small quantities of semi-liquid fecal matter of a dark brown, almost black color. Except just at the upper end of the gut, the entire intestine was thrown into numerous transverse folds; the mucosa was very pale, resembling in color ordinary hyaline cartilage very closely.

On microscopic examination the surface layer of epithelium is found for the greater part absent in the affected regions, but beginning at the mouths of the crypts the cells that line these structures appear entirely normal, with the exception only that in no part of the glands do they show mucin formation. It may be remarked, however, that mitotic figures are decidedly more frequent in the epithelial cells of the glands than is usual. On account of the pressure that is produced as a result of the presence of newly-formed fibrous tissue in the interglandular substance the lumina of the crypts have much diminished in size, and the glands from basement membrane to basement membrane often measures no more than 30μ. The elastic tissue basement membranes of the crypts show no alterations.

Notwithstanding that the surface layer of Lieberkuehn's crypts appear practically normal, the lymph node glands show very decided alterations. These changes are almost entirely confined to the bodies and basal portions of these structures, for the cells lining their necks and mouths present practically no alterations. In truth it may be stated that almost without exception the structures composing the deeper portions of the crypts have undergone necrotic change and have nearly or entirely disappeared. Filling up the area originally occupied by the glands there are numerous polymorphonuclear leucocytes, intermingled with which are a few lymphoid cells, an occasional swollen epithelial cell, and a small quantity of granular débris. The tissues of the surrounding lymph nodes contain in all instances quantities of newly-formed fibrous tissue, intermingled with the fibres of which there are numerous plasma cells, quite a number of lymphoid cells, and a few polymorphonuclear leucocytes.

In those situations where the epithelial cells have been eroded from the surface of the interglandular tissues, the structures composing them, even at their edges, present no obvious alterations; this is apparently due to the fact that in these situations there is being produced quantities of white fibrous tissue, and that this substance and the cells generating it compose the surface layers of the tissues in the diseased regions.

Deeper down between the glands great quantities of fibrous tissue is also being produced, this substance already having so increased in the diseased areas that the crypts, as has been before stated, are greatly compressed. In addition to the newly-formed white fibrous tissue, plasma cells are abundantly found, and their transformation into the so-called fibroblasts and the formation of collagenous tissue around their borders is most clearly and beautifully shown. The lymphoid cells that are always present in these situations in health have practically all been transformed into plasma cells. Here and there is found a small, ill-formed mucinoblast; these cells are much less abundant than in health. The bloodvessels in the diseased areas are sometimes slightly dilated; but we do not find here that degree of vascular change that was so pronounced in the acute changes resulting from the application of iodine. As the basal portions of the glands are approached the alterations become gradually less and less pronounced, and in the deepest portions of the mucosa newly-formed fibrous tissue is never present, though plasma cells are quite numerous. Here and there are found quite a number of lymphoid cells and a very few mucinoblasts.

The muscularis mucosæ presents no obvious alteration.

The layer of the submucosa immediately beneath the muscularis mucosæ contains numerous plasma cells, intermingled with which there are quite a number of lymphoid cells and here and there a few polymorphonuclear leucocytes. In this region there has evidently occurred a new formation of collagenous tissue to a considerable degree, the tissues being much denser than normal, and in many instances plasma cells may be seen in the process of producing this substance. The bloodvessels in the same area are somewhat more numerous and appear larger than is normally the case. Mucinoblasts are occasionally present in this layer, but are by no means so numerous as in health. Changes of a similar kind extend throughout the tissues of the submucosa, but the deeper portions do not exhibit alterations to the same degree as is found more superficially.

The other coats of the intestine present no alteration.

Résumé of the Changes in the Tissues Resulting from the Injection of Tincture of Iodine.

Where the changes are *acute*, erosion of the epithelium occurs, but the cells lining Lieberkuehn's crypts present no alterations other than that mucin formation is much diminished or entirely ceases.

The interglandular structures of the more superficial portions of the mucosa are greatly swollen as a result of the presence of quantities of effused blood, enormous dilatation of the bloodvessels, and many plasma cells; mucinoblasts are diminished in number, and when present are ill-formed and much smaller than usual.

In *chronic* poisoning by iodine the changes in the epithelial structures of the mucosa are essentially similar to those that are seen in the acute conditions, with the exception that there have occurred catarrhal changes in the lymph node glands, and around them there is usually a condition that closely resembles suppuration; surrounding the diseased area there is much newly-formed fibrous tissue.

The interglandular tissues of the surface crypts show the formation of great quantities of newly-formed white fibrous tissue. Plasma cells are in these situations numerous, and their transformation into the so-called fibroblasts and the formation of collagenous tissue around them is most exquisitely shown. The blood-vessels are but little dilated. Mucinoblasts are rarely found. In the more superficial portions of the submucosa white fibrous tissue is being formed to a considerable extent, and here again the relation of plasma cells to the production of collagenous tissue is most clear.

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